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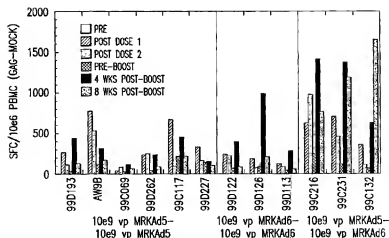
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(54) Title: METHOD OF INDUCING AN ENHANCED IMMUNE RESPONSE AGAINST HIV



(57) Abstract: An efficient means of inducing an immune response against human immunodeficiency virus (HIV) utilizing specific prime boost regimes is disclosed. The specific prime boost regimes employ a heterologous prime boost protocol employing recombinant adenoviral vectors of alternative and distinct serotypes comprising exogenous genetic material encoding a common HIV antigen. Vaccines administered into living vertebrate tissue in accordance with the disclosed regimes, preferably a mammalian host, such as a human or a non-human mammal of commercial or domestic veterinary importance, express the HIV-1 antigen (e.g., Gag), inducing a cellular immune response which specifically recognizes HIV-1. It is believed that the disclosed prime/boost regime will offer a prophylactic advantage to previously uninfected individuals and/or provide a therapeutic effect by reducing viral load levels within an infected individual, thus prolonging the asymptomatic phase of HIV-1 infection.



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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

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## TITLE OF THE INVENTION

## METHOD OF INDUCING AN ENHANCED IMMUNE RESPONSE AGAINST HIV

## 5 CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority to provisional application U.S. Serial No. 60/363,807, filed March 13, 2002, hereby incorporated by reference herein.

## STATEMENT REGARDING FEDERALLY-SPONSORED R&amp;D

10 Not Applicable

## REFERENCE TO MICROFICHE APPENDIX

Not Applicable

## 15 FIELD OF THE INVENTION

The present invention relates to an enhanced means for inducing an immune response against human immunodeficiency virus ("HIV"). Recombinant adenovirus vehicles comprising exogenous genetic material encoding a common HIV antigen are employed in a heterologous prime-boost administration. More particularly, recombina-  
20 nt adenovirus vehicles of alternative and distinct serotypes are employed in heterologous prime-boost immunization schemes. Applicants have found that administration of a recombinant adenoviral vehicle comprising exogenous genetic material encoding an HIV antigen followed by subsequent administration of a recombinant adenovirus of a different serotype comprising the antigen notably  
25 amplifies the immune response from the initial administration(s). This amplification is, further, notably higher than that observed upon utilizing the same respective recombinant adenoviral vectors independently for both priming and boosting administrations of mammalian hosts. The amplified immune response which is particularly manifest in the cellular immune response is, further, capable of  
30 specifically recognizing HIV. Viruses of use in the instant invention can be any replication-defective adenovirus, provided that the adenovirus of choice is capable of effecting expression of exogenous genetic material incorporated into the viral sequence. Based on the findings disclosed herein, it is believed that the disclosed prime/boost regime will offer a prophylactic advantage to previously uninfected

individuals and/or provide a therapeutic effect by reducing viral load levels within an infected individual, thus prolonging the asymptomatic phase of HIV-1 infection.

#### BACKGROUND OF THE INVENTION

5 Human Immunodeficiency Virus-1 (HIV-1) is the etiological agent of acquired human immune deficiency syndrome (AIDS) and related disorders. HIV-1 is an RNA virus of the Retroviridae family and exhibits the 5' LTR-*gag-pol-env*-LTR 3' organization of all retroviruses. The integrated form of HIV-1, known as the provirus, is approximately 9.8 Kb in length. Each end of the viral genome contains  
10 flanking sequences known as long terminal repeats (LTRs). The HIV genes encode at least nine proteins and are divided into three classes; the major structural proteins (Gag, Pol, and Env), the regulatory proteins (Tat and Rev); and the accessory proteins (Vpu, Vpr, Vif and Nef).

Effective treatment regimes for HIV-1 infected individuals have become  
15 available. However, these drugs will not have a significant impact on the disease in many parts of the world and they will have a minimal impact in halting the spread of infection within the human population. As is true of many other infectious diseases, a significant epidemiologic impact on the spread of HIV-1 infection will only occur subsequent to the development and introduction of an effective vaccine. There are a  
20 number of factors that have contributed to the lack of successful vaccine development to date. For instance, it is now apparent that in a chronically infected person there exists constant virus production in spite of the presence of anti-HIV-1 humoral and cellular immune responses and destruction of virally infected cells. As in the case of other infectious diseases, the outcome of disease is the result of a balance between the  
25 kinetics and the magnitude of the immune response and the pathogen replicative rate and accessibility to the immune response. Pre-existing immunity may be more successful with an acute infection than an evolving immune response can be with an established infection. A second factor is the considerable genetic variability of the virus. Although anti-HIV-1 antibodies exist that can neutralize HIV-1 infectivity in  
30 cell culture, these antibodies are generally virus isolate-specific in their activity. It has proven impossible to define serological groupings of HIV-1 using traditional methods. Rather, the virus seems to define a serological "continuum" so that individual neutralizing antibody responses, at best, are effective against only a handful of viral variants. Given this latter observation, it would be useful to identify

immunogens and related delivery technologies that are likely to elicit anti-HIV-1 cellular immune responses. It is known that in order to generate CTL responses antigen must be synthesized within or introduced into cells, subsequently processed into small peptides by the proteasome complex, and translocated into the endoplasmic reticulum/Golgi complex secretory pathway for eventual association with major histocompatibility complex (MHC) class I proteins. CD8<sup>+</sup> T lymphocytes recognize antigen in association with class I MHC via the T cell receptor (TCR) and the CD8 cell surface protein. Activation of naive CD8<sup>+</sup> T cells into activated effector or memory cells generally requires both TCR engagement of antigen as described above as well as engagement of costimulatory proteins. Optimal induction of CTL responses usually requires "help" in the form of cytokines from CD4<sup>+</sup> T lymphocytes which recognize antigen associated with MHC class II molecules via TCR and CD4 engagement.

Adenoviral vectors have been developed as live viral vectors for the delivery and expression of various foreign antigens including HIV and have proven to be effective in eliciting a significant CTL response in treated individuals. Adenoviruses are non-enveloped viruses containing a linear double-stranded genome of about 36 kb. The vectors achieve high viral titres, have a broad cell tropism, and can infect nondividing cells. Adenoviral vectors are very efficient gene transfer vehicles and are frequently used in clinical gene therapy studies. In addition, adenovirus has formed the basis of many promising viral immunization protocols.

European Patent Applications 0 638 316 (Published February 15, 1995) and 0 586 076 (Published March 9, 1994), (both assigned to American Home Products Corporation) describe replicating adenovirus vectors carrying an HIV gene, including *env* or *gag*. Various treatment regimes based on these vectors were used with chimpanzees and dogs, some of which included booster adenovirus or protein plus alum treatments.

Replication-defective adenoviral vectors harboring deletions, for instance, in the E1 region constitute a safer alternative to their replicating counterparts. Recent adenoviral vectors have incorporated the known packaging repeats into these vectors; e.g., see EP 0 707 071, disclosing, *inter alia*, an adenoviral vector deleted of E1 sequences from base pairs 459 to 3328; and U.S. Patent No. 6,033,908, disclosing, *inter alia*, an adenoviral vector deleted of base pairs 459-3510. The packaging efficiency of adenovirus has been taught to depend on the number of incorporated

individual A (packaging) repeats; *see, e.g.*, Gräble and Hearing, 1990 *J. Virol.* 64(5):2047-2056; Gräble and Hearing, 1992 *J. Virol.* 66(2):723-731.

Adenovirus serotypes 5 and 6 have been disclosed and are publicly available (*see*, American Type Culture Collection ("ATCC") Accession Deposit Nos. VR-5 and VR-6; respectively). The wildtype adenovirus serotype 5 sequence is, further, known and described in the art; *see*, Chroboczek *et al.*, 1992 *J. Virology* 186:280-5. The complete sequence for adenovirus serotype 6, which is provided in Figures 11A-1 to 11A-14, was first disclosed in copending U.S. Provisional Application Serial No. 60/328,655, filed on October 11, 2001. Adenovirus serotype 6, as serotype 5, has been described previously in the literature; *see* Rowe *et al.*, 1953 *Proc. Soc. Exp. Biol. Med.* 84:570; Rowe *et al.*, 1955 *Am. J. Hyg.* 61:197-218; and Hierholzer *et al.*, 1991 *Arch. Virol.* 121:179-97. Adenovirus serotypes other than Ad5 and Ad6 are also known and described in the literature.

Administration protocols employing viral vaccine vectors to date have employed various prime-boost inoculation schemes. Two general schemes frequently used are: (1) wherein both priming and boosting of the mammalian host is accomplished using the same virus vehicle, and (2) wherein the priming and boosting is carried out utilizing different vehicles not necessarily limited to virus vehicles. Examples of the latter are, for instance, a scheme composed of a DNA prime and viral boost, and one composed of a viral prime and a viral boost wherein alternate virus are used.

It would be of great import in the battle against AIDS to develop a prophylactic- and/or therapeutic-based HIV vaccine strategy capable of generating a strong cellular immune response against HIV infection. The present invention addresses and meets these needs by disclosing a heterologous prime-boost HIV immunization regime based on the administration of recombinant adenoviral vectors of alternative and distinct serotypes, wherein the recombinant adenoviral vectors comprise exogenous genetic material encoding a common HIV antigen. One aspect of the instant invention concerns heterologous immunization schemes employing recombinant adenoviral vectors derived from adenovirus serotypes 5, 6, and 35. A vaccine protocol in accords with this description, as far as Applicants are aware, has not been demonstrated for HIV. This vaccine prime-boost regime may be administered to a host, such as a human.

## SUMMARY OF THE INVENTION

The present invention relates to an enhanced method for generating an immune response against human immunodeficiency virus ("HIV"). The method is based on the heterologous prime-boost administration of recombinant adenovirus vehicles of alternative and distinct serotypes comprising heterologous genetic material encoding an HIV antigen to effect a more pronounced immune response against HIV than that which can be obtained by either vector independently in a single modality prime-boost immunization scheme. In accordance with the disclosed methods, a mammalian host is first administered a priming dose comprising a recombinant adenoviral vector of a first serotype comprising a gene encoding an HIV antigen and, after a period of time, administered a boosting dose comprising a recombinant adenoviral vector of a second and different serotype carrying the gene encoding the HIV antigen. There may be a predetermined minimum amount of time separating the administrations, which time essentially allows for an immunological rest. In particular embodiments, this rest is for a period of at least 4 months. Multiple primings typically, 1-4, are usually employed, although more may be used. The length of time between priming and boost may typically vary from about four months to a year, but other time frames may be used. Applicants have found that boosting of the adenovirus-primed response with an adenovirus of an alternative and distinct serotype leads to a notably amplified immune response to the HIV antigen. Thus the instant invention relates to the administration of alternate serotype adenovirus HIV vaccines in accordance with the disclosed methods.

Accordingly, the instant invention relates to a method for inducing an enhanced immunological response against an HIV-1 antigen in a mammalian host comprising the steps of (a) inoculating the mammalian host with a recombinant adenoviral vector of a first serotype which is at least partially deleted in E1 and devoid of E1 activity comprising a gene encoding an HIV-1 antigen or an immunologically relevant modification thereof; and thereafter (b) inoculating the mammalian host with a boosting immunization comprising a recombinant adenoviral vector of a second and different serotype at least partially deleted in E1 and devoid of E1 activity comprising a gene encoding an HIV-1 antigen or immunologically relevant modification thereof.

The recombinant adenoviral vectors used in the immunization regimes of the present invention may comprise any replication-defective adenoviral vector which is

genetically stable through large-scale production and purification of the virus. In other words, a recombinant adenoviral vector suitable for use in the methods of the instant invention can be any purified recombinant replication-defective virus shown to be genetically stable through multiple passages in cell culture which remains so during large-scale production and purification procedures. Such a recombinant virus vector and harvested virus vaccine lends itself to large scale dose filling and subsequent worldwide distribution procedures which will be demanded of an efficacious monovalent or multivalent HIV vaccine. The present invention meets this basic requirement with description of an immunization regime which is based on the use of recombinant replication-defective adenovirus serotypes examples but not limitations of which include serotypes 5, 6, and 35.

Adenoviral vectors preferred for use in the immunization regimes of the instant invention are those that are at least partially deleted in E1 and devoid of E1 activity. Vectors in accordance with this description can be readily propagated in E1-complementing cell lines, such as PER.C6® cells.

The recombinant adenoviral vectors of use in the instant application whether intended as the priming or boosting vehicle must comprise a gene encoding an HIV antigen. In specific embodiments, the gene encoding the HIV antigen or immunologically relevant modification thereof comprises codons optimized for expression in a mammalian host (*e.g.*, a human). Recombinant adenoviral vectors of use in the methods of the instant invention can comprise a gene expression cassette comprising (a) nucleic acid encoding an HIV antigen (*e.g.*, an HIV protein) or biologically active and/or immunologically relevant portion thereof; (b) a heterologous (non-native) or modified native promoter operatively linked to the nucleic acid of part a); and, (c) a transcription termination sequence. A heterologous promoter can be any promoter under the sun (modified or not) which is not native to, or derived from, the virus in which it will be used.

HIV antigens of use in the instant invention include the various HIV proteins, immunologically relevant modifications, and immunogenic portions thereof. The present invention, thus, encompasses the various forms of codon-optimized HIV-1 gag (including but by no means limited to p55 versions of codon-optimized full length ("FL") Gag and tPA-Gag fusion proteins), HIV-1 pol, HIV-1 nef, HIV-1 env, fusions of the above constructs, and selected modifications of the above possessing immunological relevance. Examples of HIV-1 Gag, Pol, Env, and/or Nef fusion

proteins include but are not limited to fusion of a leader or signal peptide at the NH<sub>2</sub>-terminal portion of the viral antigen coding region. Such a leader peptide includes but is not limited to a tPA leader peptide.

5 Recombinant viral vectors in accordance with the instant disclosure form an aspect of the instant invention. Other aspects of the instant invention are host cells comprising said adenoviral vectors; vaccine compositions comprising said vectors; and methods of producing the vectors comprising (a) introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and (b) harvesting the resultant adenoviral vectors.

10 The present invention also relates to prime-boost regimes wherein the recombinant adenoviral vectors comprise various combination of the above HIV antigens. Such HIV immunization regimes will provide for an enhanced cellular immune response subsequent to host administration, particularly given the genetic diversity of human MHCs and of circulating virus. Examples, but not limitations,  
15 include viral vector-based multivalent vaccine compositions which provide for a divalent (*e.g.*, gag and nef, gag and pol, or pol and nef components) or a trivalent vaccine (*e.g.*, gag, pol and nef components) composition. Such a multivalent vaccine may be filled for a single dose or may consist of multiple inoculations of each individually filled component. To this end, preferred vaccine compositions of use in  
20 the methods of the instant application are recombinant adenovirus vectors comprising multiple, distinct HIV antigen classes. Each HIV antigen class is subject to sequence manipulation, thus providing for a multitude of potential vaccine combinations; and such combinations are within the scope of the present invention. The utilization of such combined modalities increase the probability of eliciting an even more potent  
25 cellular immune response when compared to inoculation with a single modality regime.

The concept of a "combined modality" as disclosed herein also covers the alternative mode of administration whereby multiple HIV-1 viral antigens may be ligated into a proper shuttle plasmid for generation of a recombinant viral vector  
30 comprising multiple open reading frames. For example, a trivalent vector may comprise a gag-pol-nef fusion, or possibly a "2+1" divalent vaccine comprising, for instance, a gag-pol fusion (*i.e.*, codon optimized p55 gag and inactivated optimized pol) within the same backbone, with each open reading frame being operatively linked to a distinct promoter and transcription termination sequence. Alternatively, the

two open reading frames may be operatively linked to a single promoter, with the open reading frames operatively linked by an internal ribosome entry sequence (IRES).

Administration of the recombinant adenoviral vectors via the disclosed heterologous means provides for improved cellular-mediated immune responses; responses more pronounced than that afforded by single modality regimes. An effect of the improved vaccine should be a lower transmission rate to previously uninfected individuals (i.e., prophylactic applications) and/or reduction in the levels of the viral loads within an infected individual (i.e., therapeutic applications), so as to prolong the asymptomatic phase of HIV-1 infection. The administration, intracellular delivery and expression of the vaccine in this manner elicits a host CTL and Th response. The individual vaccinee or mammalian host (as referred to herein) can be a primate (both human and non-human) as well as any non-human mammal of commercial or domestic veterinary importance.

In light hereof, the present invention relates to methodology regarding administration of the recombinant adenoviral HIV vaccines to provide effective immunoprophylaxis, to prevent establishment of an HIV-1 infection following exposure to this virus, or as a post-HIV infection therapeutic vaccine to mitigate the acute HIV-1 infection so as to result in the establishment of a lower virus load with beneficial long term consequences. Such treatment regimes may include a monovalent or multivalent composition, and/or various combined modality applications. Therefore, the present invention provides for methods of using the disclosed HIV vaccine administration scheme within the various parameters disclosed herein as well as any additional parameters known in the art which, upon introduction into mammalian tissue, induces intracellular expression of the HIV antigen(s) and an effective immune response to the respective HIV antigen(s).

To this end, the present invention relates in part to methods of generating a cellular immune response in a vaccinee, preferably a human vaccinee, wherein the individual is given the recombinant adenovirus HIV vaccines in the manner described.

As used throughout the specification and claims, the following definitions and abbreviations are used:

"HAART" refers to -- highly active antiretroviral therapy --.

"first generation" vectors are characterized as being replication-defective. They typically have a deleted or inactivated E1 gene region, and often have a deleted or inactivated E3 gene region as well.

"AEX" refers to Anion Exchange chromatography.

5 "QPA" refers to Quick PCR-based Potency Assay.

"bps" refers to base pairs.

"s" or "str" denotes that the transgene is in the E1 parallel or "straight" orientation.

"PBMCs" refers to peripheral blood monocyte cells.

10 "FL" refers to full length.

"FLgag" refers to a full-length optimized gag gene, as shown in Figure 2.

"Ad5-Flgag" refers to an adenovirus serotype 5 replication-deficient virus which carries an expression cassette which comprises a full length optimized gag gene under the control of a CMV promoter.

15 "Promoter" means a recognition site on a DNA strand to which an RNA polymerase binds. The promoter forms an initiation complex with RNA polymerase to initiate and drive transcriptional activity. The complex can be modified by activating sequences such as enhancers or inhibiting sequences such as silencers.

20 "Leader" means a DNA sequence at the 5' end of a structural gene which is transcribed along with the gene. This usually results in a protein having an N-terminal peptide extension, often referred to as a pro-sequence.

"Intron" means a section of DNA occurring in the middle of a gene which does not code for an amino acid in the gene product. The precursor RNA of the intron is excised and therefore not transcribed into mRNA or translated into protein.

25 "Immunologically relevant" or "biologically active," when used in the context of a viral protein, means that the protein is capable, upon administration, of eliciting a measurable immune response within an individual sufficient to retard the propagation and/or spread of the virus and/or to reduce the viral load present within the individual. The same terms, when used in the context of a nucleotide sequence, means that the sequence is capable of encoding for a protein capable of the above.

30 "Cassette" refers to a nucleic acid sequence which is to be expressed, along with its transcription and translational control sequences. By changing the cassette, a vector can express a different sequence.

"bGHpA" refers to a bovine growth hormone transcription terminator/polyadenylation sequence.

"tPAgag" refers to a fusion between the tissue plasminogen activator leader sequence and an optimized HIV gag gene.

5 Where utilized, "IA" or "inact" refers to an inactivated version of a gene (e.g. IApol).

"MCS" is "multiple cloning site".

"Ad5" is adenovirus of serotype 5.

"Ad6" is adenovirus of serotype 6.

10 In general, adenoviral constructs, gene constructs are named by reference to the genes contained therein. For example:

"Ad5 HIV-1 gag", also referred to as the original HIV-1 gag adenoviral vector, is a vector containing a transgene cassette composed of a hCMV intron A promoter, the full length version of the human codon-optimized HIV-1 gag gene, and  
15 the bovine growth hormone polyadenylation signal.

"MRK Ad5 HIV-1 gag" also referred to as "MRKAd5gag" or "Ad5gag2" is an adenoviral vector which is deleted of E1, and contains adenoviral base pairs 1-450 and 3511-3523, with a human codon-optimized HIV-1 gag gene in an E1 parallel orientation under the control of a CMV promoter without intron A. The construct  
20 also comprises a bovine growth hormone polyadenylation signal.

"pV1JnsHIVgag", also referred to as "HIVFLgagPR9901", is a plasmid comprising the CMV immediate-early (IE) promoter and intron A, a full-length codon-optimized HIV gag gene, a bovine growth hormone-derived polyadenylation and transcriptional termination sequence, and a minimal pUC backbone.

25 "pV1JnsCMV(no intron)-FLgag-bGHpA" is a plasmid derived from pV1JnsHIVgag which is deleted of the intron A portion of CMV and which comprises the full length HIV gag gene. This plasmid is also referred to as "pV1JnsHIVgag-bGHpA", pV1Jns-hCMV-FL-gag-bGHpA" and "pV1JnsCMV(no intron) + FLgag + bGHpA".

30 "pV1JnsCMV(no intron)-FLgag-SPA" is a plasmid of the same composition as pV1JnsCMV(no intron)-FLgag-bGHpA except that the SPA termination sequence replaces that of bGHpA. This plasmid is also referred to as "pV1Jns-HIVgag-SPA" and pV1Jns-hCMV-FLgag-SPA".

- "pdelE1sp1A" is a universal shuttle vector with no expression cassette (i.e., no promoter or polyA). The vector comprises wildtype adenovirus serotype 5 (Ad5) sequences from bp 1 to bp 341 and bp 3524 to bp 5798, and has a multiple cloning site between the Ad5 sequences ending 341 bp and beginning 3524 bp. This plasmid is also referred to as the original Ad 5 shuttle vector.
- "MRKpdelE1sp1A" or "MRKpdeIE1(Pac/pIX/pack450)" or "MRKpdeIE1(Pac/pIX/pack450)Cla1" is a universal shuttle vector with no expression cassette (i.e. no promoter or polyA) comprising wildtype adenovirus serotype 5 (Ad5) sequences from bp 1 to bp 450 and bp 3511 to bp 5798. The vector has a multiple cloning site between the Ad5 sequence ending 450 bp and beginning 3511 bp. This shuttle vector may be used to insert the CMV promoter and the bGHpA fragments in both the straight ("str". or E1 parallel) orientation or in the opposite (opp. or E1 antiparallel) orientation.
- "MRKpdeIE1(Pac/pIX/pack450)+CMVmin+bGHpA(str.\*)" is still another shuttle vector which is the modified vector that contains the CMV promoter (no intron A) and the bGHpA fragments. The expression unit containing the hCMV promoter (no intron A) and the bovine growth hormone polyadenylation signal has been inserted into the shuttle vector such that insertion of the gene of choice at a unique *Bgl*III site will ensure the direction of transcription of the transgene will be Ad5 E1 parallel when inserted into the MRKpAd5(E1/E3+)Cla1 pre-plasmid.
- "MRKpdeIE1-CMV(no intron)-FLgag-bGHpA" is a shuttle comprising Ad5 sequences from base pairs 1-450 and 3511-5798, with an expression cassette containing human CMV without intron A, the full-length human codon-optimized HIV gag gene and bovine growth hormone polyadenylation signal. This plasmid is also referred to as "MRKpdeIE1 shuttle +hCMV-FL-gag-BGHpA"
- "MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA" is an adenoviral vector comprising all Ad5 sequences except those nucleotides encompassing the E1 region (from 451-3510), a human CMV promoter without intron A, a full-length human codon-optimized HIV gag gene, and a bovine growth hormone polyadenylation signal. This vector is also referred to as "MRKpAdHVE3 + hCMV-FL-gag-BGHpA", "MRKpAd5HIV-1gag", "MRKpAd5gag", "pMRKAd5gag" or "pAd5gag2".

## BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows the HIV-1 gag adenovector "Ad5 HIV-1 gag". This vector is disclosed in PCT International Application No. PCT/US00/18332 (WO 01/02607) filed July 3, 2000, claiming priority to U.S. Provisional Application Serial No.

5 60/142,631, filed July 6, 1999, and U.S. Application Serial No. 60/148,981, filed August 13, 1999, all three applications which are hereby incorporated by reference.

Figure 2 shows the nucleic acid sequence (SEQ ID NO: 1) of the optimized human HIV-1 gag open reading frame.

Figure 3 shows diagrammatically the transgene construct disclosed in PCT  
10 International Application No. PCT/US01/28861, filed September 14, 2001 in comparison with the original gag transgene. PCT International Application No. PCT/US01/28861 claims priority to U.S. Provisional Application Serial Nos. 60/233,180, 60/279,056, and 60/317,814, filed September 15, 2000, March 27, 2001, and September 7, 2001, respectively; the above applications all of which are hereby  
15 incorporated by reference.

Figure 4 shows the modifications made to the adenovector backbone of Ad5HIV-1gag in the generation of the vector disclosed in PCT International Application No. PCT/US01/28861 which is utilized in certain examples of the instant application.

20 Figure 5 shows the levels of Gag-specific T cells in rhesus macaques immunized with (a) two priming doses of 10e9 vp of MRKAd5 HIV-1 gag and a single booster shot with 10e9 vp MRKAd5 HIV-1 gag ("10e9 vp MRKAd5-10e9 vp MRKAd5"); (b) two priming doses of 10e9 pfu MRKAd6 HIV-1 gag and a single  
25 booster with 10e9 pfu MRKAd6 HIV-1 gag ("10e9 pfu MRKAd6-10e9 pfu MRKAd6"); or (c) two priming doses of 10e9 vp of MRKAd5 HIV-1 gag followed by a single booster shot with 10e9 pfu MRKAd6 HIV-1 gag ("10e9 vp MRKAd5-10e9 pfu MRKAd6"). The levels expressed as number of spot-forming cells (SFC) per million PBMC are the mock-corrected values for each animal prior to the start of the immunization regimen ("Pre"); 4 weeks after the first priming dose ("Post Dose 1"); 4  
30 weeks after the second priming dose ("Post Dose 2"); just prior to the boost ("Pre-Boost"); 4 weeks after the boost ("4 wks Post-Boost"); and 8 weeks after the boost ("8 wks Post-Boost").

Figure 6 shows the Gag-specific T cell responses induced by two priming doses of 10e7 vp dose of MRKAd5 HIV-1 gag (week 0; week 4) followed by

administration of  $10^7$  vp MRKAd6 HIV-1 gag at week 27. The levels provided are the mock-corrected levels for each animal prior to the start of the immunization regimen ("Pre"); 4 weeks after the first priming dose ("Post Dose 1"); 4 weeks after the second priming dose ("Post Dose 2"); just prior to the boost ("Pre-Boost"); 4 weeks after the boost ("4 wks Post-Boost"); and 8 weeks after the boost ("8wks Post-Boost"). One will note a significant increase compared to the levels just prior to the boost. MRKAd6 HIV-1 gag elicited a large amplification of the priming response. The post-boost increases shown are largely attributed to the expansion of memory T cells instead of priming of new lymphocytes.

Figure 7 shows the homologous recombination protocol utilized to recover pAdE1-E3 disclosed herein.

Figure 8 shows a restriction map of the pMRKAd5HIV-1gag vector.

Figures 9A-1 to 9A-45 show the nucleotide sequence of the pMRKAd5HIV-1gag vector (SEQ ID NO:2 [coding] and SEQ ID NO:3 [non-coding]).

Figure 10 shows the levels of Gag-specific antibodies in rhesus macaques immunized with (a) two priming doses of  $10^9$  vp of MRKAd5 HIV-1 gag and a single booster shot with  $10^9$  vp MRKAd5 HIV-1 gag (" $10^9$  vp MRKAd5- $10^9$  vp MRKAd5"), (b) two priming doses of  $10^9$  pfu MRKAd6 HIV-1 gag and a single booster with  $10^9$  pfu MRKAd6 HIV-1 gag (" $10^9$  pfu MRKAd6- $10^9$  pfu MRKAd6"), or (c) two priming doses of  $10^9$  vp of MRKAd5 HIV-1 gag followed by a single booster shot with  $10^9$  pfu MRKAd6 HIV-1 gag (" $10^9$  vp MRKAd5- $10^9$  pfu MRKAd6"). Shown are the geometric mean titers for each cohort at the start of the immunization regimen ("Pre"), 4 weeks after the first priming dose ("Wk 4"), 4 weeks after the second priming dose ("Wk 8"), just prior to the boost ("Pre-Boost"), and 8 weeks after the boost ("Post-Boost").

Figures 11A-1 to 11A-14 show the nucleic acid sequence for the Ad6 genome (SEQ ID NO:5).

Figure 12 shows the basic genomic organization of Ad6. The linear (35759 bp) double-stranded DNA genome is indicated by two parallel lines and is divided into 100 map units. Transcription units are shown relative to their position and orientation in the genome. Early genes (E1A, E1B, E2A/B, E3 and E4) are indicated by gray bars. Late genes (L1 to L5), indicated by black bars, are produced by alternative splicing of a transcript produced from the major late promoter (MLP) and all contain the tripartite leader (1, 2, 3) at their 5' ends.

Figure 13 shows the homologous recombination protocol utilized to recover pMRKAd6E1-.

#### DETAILED DESCRIPTION OF THE INVENTION

5 An enhanced means for generating an immune response against human immunodeficiency virus ("HIV") is described. The disclosed methods employ a combination of recombinant adenovirus gene delivery vehicles of alternative and distinct serotypes in the administration of exogenous genetic material encoding an HIV antigen (or antigens) of interest. In accordance with the methods of the instant  
10 invention, a priming dose of the HIV antigen(s) is first delivered with a recombinant adenoviral vector of a first serotype. This dose effectively primes the immune response so that, upon subsequent identification of the antigen in the circulating immune system, the immune response is capable of immediately recognizing and responding to the antigen within the host. The priming dose(s) is then followed up  
15 with a boosting dose of a second and different adenovirus serotype comprising exogenous genetic material encoding the antigen. In one aspect of the instant invention, a mammalian host is first administered a priming dose(s) comprising a recombinant adenoviral vector of serotype 5 or 6 and then administered a subsequent  
20 boosting dose(s) comprising a recombinant adenoviral vector of a different serotype (*i.e.*, a serotype other than that used in the priming administration; examples, but not limitations of which include Ad35. Very specific embodiments encompassed herein are wherein (1) an Ad5-primed response is boosted with a recombinant Ad6 vehicle comprising an HIV antigen; (2) an Ad6-primed response is boosted with a  
25 recombinant Ad5 vehicle comprising an HIV antigen; (3) an Ad5/Ad6-primed response is boosted with a recombinant, Ad35-based vehicle; and (4) an Ad35-primed response is boosted with a recombinant, an Ad5/Ad6-based vehicle. As relates to HIV antigens, administration in accordance with the methods of the instant invention results in a significant non-additive synergistic effect which notably increases the immune response seen in inoculated mammalian hosts. The effects are particularly  
30 evident in the cellular immune responses generated following inoculation. The disclosed immunization regime, thus, offers a prophylactic advantage to previously uninfected individuals and can offer a therapeutic effect to reduce viral load levels in those already infected with the virus, thus prolonging the asymptomatic phase of HIV-1 infection.

Accordingly, the instant invention relates to a method for inducing an enhanced immunological response against an HIV-1 antigen in a mammalian host comprising the steps of (a) inoculating the mammalian host with a recombinant adenoviral vector of a first serotype at least partially deleted in E1 and devoid of E1 activity comprising a gene encoding an HIV-1 antigen or immunologically relevant modification thereof; and thereafter (b) inoculating the mammalian host with a boosting immunization comprising a recombinant adenovirus vector of a second and distinct serotype at least partially deleted in E1 and devoid of E1 activity comprising a gene encoding an HIV-1 antigen or immunologically relevant modification thereof.

Preferred embodiments of the instant invention employ adenoviral vectors which are replication-defective by reason of having a deletion in the E1 region which renders the vector devoid (or essentially devoid) of E1 activity. Adenovirus serotype 5 has been found to be a very effective adenovirus vehicle for purposes of effectuating sufficient expression of exogenous genetic material encoding HIV-specific antigens in order to provide for sufficient priming of the mammalian host immune response. It has further been found and disclosed herein that recombinant adenovirus serotype 6 is capable of very effectively boosting the adenovirus serotype 5-primed response. In an alternative scenario, recombinant adenovirus serotype 5 can be used to boost an adenovirus serotype 6-primed response. These findings have also been demonstrated with adenovirus vehicles of different subgroups, for instance, Ad5/6-prime (subgroup C)/Ad35-boost (subgroup B).

The wildtype adenovirus serotype 5 sequence is known and described in the art; *see*, Chroboczek *et al.*, 1992 *J. Virology* 186:280, which is hereby incorporated by reference. Accordingly, a particular embodiment of the instant invention is an immunization scheme employing an adenovirus vehicle based on the wildtype adenovirus serotype 5 sequence in the priming or boosting administration; a virus of which is on deposit with the American Type Culture Collection ("ATCC") under ATCC Deposit No. VR-5. One of skill in the art can, however, readily identify alternative and distinct adenovirus serotypes (e.g., serotypes 2, 4, 6, 12, 16, 17, 24, 31, 33, and 42) and incorporate same in the disclosed heterologous prime-boost immunization schemes. The sequence of adenovirus serotype 6 (ATCC Deposit No. VR-6) is extremely homologous (approximately 98%) at the nucleic acid level to the sequence of adenovirus serotype 5, with relatively few base pair differences in the approximate 36 kb sequences. The genomic organization of Ad6 is also very similar;

see Figure 12. Chimeric Ad5/Ad6 constructs which retain the serotype-determining epitopes of either Ad5 or Ad6 are also suitable for use in the instant invention; provided that the serotype determining epitopes are distinct from the adenovirus vehicle used in combination therewith (*i.e.*, that the determinants are distinct from the vehicle used in the priming dose if the chimera is utilized in the boosting dose, and *vice versa*). It is important to the overall functioning of the disclosed methods that the serotypes of the priming and boosting vectors be distinct.

Recombinant adenoviral vectors comprising deletions additional to that contained within the region of E1 are also contemplated for use within the methods of the instant invention. For example, vectors comprising deletions in both E1 and E3 are contemplated for use within the methods of the instant invention. Such a vector can accommodate a larger amount of foreign DNA (or exogenous genetic material).

Adenoviral vectors of use in the methods of the instant invention can be constructed using known techniques, such as those reviewed in Hitt *et al.*, 1997 "Human Adenovirus Vectors for Gene Transfer into Mammalian Cells" *Advances in Pharmacology* 40:137-206, which is hereby incorporated by reference. Often, a plasmid or shuttle vector is generated which comprises sequence from the specific adenovirus of interest. This process is described in Hitt *et al.*, *supra*.

Adenoviral pre-plasmids (*e.g.*, pMRKAd5gag and pMRKAd6gag) can be generated by homologous recombination using adenovirus backbones (*e.g.*, MRKAd5HVE3 and pMRKAd6E1-, an Ad6 genome plasmid) and the appropriate shuttle vector. The resultant plasmids in linear form, are capable of replication after entering the PER.C6<sup>®</sup> cells or other complementing cell line, and virus is produced. The infected cells and media are then harvested after viral replication is complete.

Viral vectors can be propagated in various E1 complementing cell lines, including the known cell lines 293 and PER.C6<sup>®</sup>. Both these cell lines express the adenoviral E1 gene product. PER.C6<sup>®</sup> is described in WO 97/00326 (published January 3, 1997) and issued U.S. Patent No. 6,033,908, both of which are hereby incorporated by reference. It is a primary human retinoblast cell line transduced with an E1 gene segment that complements the production of replication deficient (FG) adenovirus, but is designed to prevent generation of replication competent adenovirus by homologous recombination. Cells of particular interest have been stably transformed with a transgene that encodes the AD5E1A and E1B gene, like PER.C6<sup>®</sup>, from 459 bp to 3510 bp inclusive. 293 cells are described in Graham *et al.*, 1977 J.

*Gen. Virol* 36:59-72, which is hereby incorporated by reference. As stated above, due consideration must be given to the adenoviral sequences present in the complementing cell line used. It is preferred that the sequences not overlap with that present in the vector if the possibility of recombination is to be minimized.

5       The recombinant adenoviral vectors of use in the instant invention comprise a gene encoding any antigen, but particularly, an HIV-1 antigen or an immunologically relevant modification thereof. HIV antigens of interest include, but are not limited to, the major structural proteins of HIV such as Gag, Pol, and Env, immunologically relevant modifications, and immunogenic portions thereof. The invention, thus,  
10       encompasses the various forms of codon-optimized HIV-1 gag (including but by no means limited to p55 versions of codon-optimized full length ("FL") Gag and tPA-Gag fusion proteins), HIV-1 pol, HIV-1 nef, HIV-1 env, and selected modifications of immunological relevance.

15       Exogenous genetic material encoding a protein of interest may exist in the form of an expression cassette. A gene expression cassette preferably comprises (a) a nucleic acid encoding a protein of interest; (b) a heterologous (non-native) or modified native promoter operatively linked to the nucleic acid encoding the protein; and (c) a transcription termination sequence.

20       The transcriptional promoter is preferably recognized by an eukaryotic RNA polymerase. In a preferred embodiment, the promoter is a "strong" or "efficient" promoter. An example of a strong promoter is the immediate early human cytomegalovirus promoter (Chapman et al, 1991 *Nucl. Acids Res.* 19:3979-3986, which is incorporated by reference); in certain embodiments without intronic sequences. Specific embodiments of the instant invention employ human CMV  
25       promoters without intronic sequences, like intron A. Applicants have found that intron A, a portion of the human cytomegalovirus promoter (hCMV), constitutes a region of instability for adenoviral vectors. CMV without intron A has been found to effectuate comparable expression capabilities *in vitro* when driving HIV gag expression and, furthermore, behaved equivalently to intron A-containing constructs  
30       in Balb/c mice *in vivo* with respect to their antibody and T-cell responses at both dosages of plasmid DNA tested (20 µg and 200 µg). Those skilled in the art will appreciate that any of a number of other known promoters, such as the strong immunoglobulin, or other eukaryotic gene promoters may also be used, including the EF1 alpha promoter, the murine CMV promoter, Rous sarcoma virus (RSV)

promoter, SV40 early/late promoters and the beta-actin promoter. In certain embodiments, the promoter may also comprise a regulatable sequence such as the Tet operator sequence. This would be extremely useful, for example, in cases where the gene products are effecting a result other than that desired and repression is sought.

5 Preferred transcription termination sequences present within the gene expression cassette are the bovine growth hormone terminator/polyadenylation signal (bGHpA) and the short synthetic polyA signal (SPA) of 50 nucleotides in length, defined as follows: AATAAAAGATCITTATTTTCATTAGATCTGTGTGTTGGT-TTTTGTGTG (SEQ ID NO:4). The combination of the CMV promoter (devoid of

10 the intron A region) with the BGH terminator constitutes a specific embodiment of the present invention, although other promoter/terminator combinations can be used. Certain embodiments may incorporate a leader or signal peptide into the transgene. A preferred leader is that from the tissue-specific plasminogen activator protein, tPA.

In accordance with the methods of the instant invention, the expression of

15 exogenous HIV genetic material should elicit potent and broad cellular immune responses against HIV that will either lessen the likelihood of persistent virus infection and/or lead to the establishment of a clinically significant lowered virus load subject to HIV infection or in combination with HAART therapy, mitigate the effects of previously established HIV infection (antiviral immunotherapy(ARI)). While any

20 HIV antigen (e.g., gag, pol, nef, gp160, gp41, gp120, tat, rev, etc.) may be incorporated into the recombinant adenoviral vectors of use in the instant invention, preferred embodiments include the codon optimized p55 gag antigen, pol and nef. The adenoviral vehicles of the instant invention can utilize heterologous nucleic acid which may or may not be codon-optimized. In specific embodiments of the instant

25 invention, the individual can be primed with an adenoviral vector comprising codon-optimized heterologous nucleic acid, and boosted with an adenovirus of an alternative serotype comprising non-codon-optimized nucleic acid. Administration of multiple antigens possesses the possibility for exploiting various different combinations of codon-optimized and non-codon-optimized sequences.

30 Sequences based on different Clades of HIV-1 are suitable for use in the instant invention, most preferred of which are Clade B and Clade C. Particularly preferred embodiments are those sequences (especially, codon-optimized sequences) based on consensus Clade B sequences. Preferred versions of the viral vaccines will encode modified versions of pol or nef. Preferred embodiments of the viral vaccines

carrying HIV envelope genes and modifications thereof comprise the HIV codon-optimized *env* sequences of PCT International Applications PCT/US97/02294 and PCT/US97/10517, published August 28, 1997 (WO 97/31115) and December 24, 1997, respectively; both documents of which are hereby incorporated by reference.

- 5 Sequences for many genes of many HIV strains are publicly available in GENBANK and primary, field isolates of HIV are available from the National Institute of Allergy and Infectious Diseases (NIAID) which has contracted with Quality Biological (Gaithersburg, MD) to make these strains available. Strains are also available from the World Health Organization (WHO), Geneva Switzerland. It is  
10 preferred that the gag gene be from an HIV-1 strain (CAM-1; Myers et al, eds. "Human Retroviruses and AIDS: 1995, IIA3-IIA19, which is hereby incorporated by reference). This gene closely resembles the consensus amino acid sequence for the clade B (North American/European) sequence. Therefore, it is within the purview of the skilled artisan to choose an appropriate nucleotide sequence which encodes a  
15 specific HIV gag antigen, or immunologically relevant portion thereof. A clade B or clade C based p55 gag antigen will potentially be useful on a global scale. A transgene of choice for insertion into the vectors utilized within the disclosed methods is a codon-optimized version of p55 gag.

- In addition to a single HIV antigen of interest being delivered by the  
20 recombinant adenoviral vectors, two or more antigens can be delivered either via separate vehicles or delivered *via* the same vehicle. For instance, a priming dose in accordance with the instant invention can comprise a recombinant adenoviral vector of a first serotype comprising genes encoding both nef and pol or, alternatively, two or more alternative HIV-1 antigens. The boosting dose could then comprise a  
25 recombinant adenoviral vector of a second and different serotype comprising the genes encoding both nef and pol (or whichever two or more HIV-1 antigens were used in the priming dose). In an alternative scenario, the priming dose can comprise a mixture of separate adenoviral vehicles each comprising a gene encoding for a different HIV-1 antigen. In such a case, the boosting dose could also comprise a  
30 mixture of vectors each comprising a gene encoding for a separate HIV-1 antigen, provided that the boosting dose(s) administers recombinant viral vectors comprising genetic material encoding for the same or a similar set of antigens that were delivered in the priming dose(s). These divalent (*e.g.*, gag and nef, gag and pol, or pol and nef components, for instance) or trivalent (*e.g.*, gag, pol and nef components, for instance)

vaccines can further be administered by a combination of the techniques described above. Therefore, a preferred aspect of the present invention are the various vaccine formulations that can be administered by the methods of the instant invention. It is also within the scope of the present invention to embark on combined modality regimes which include multiple but distinct components from a specific antigen.

The disclosed immunization regimes employing fusion constructs composed of two or more antigens are also encompassed herein. For example, multiple HIV-1 viral antigens may be ligated into a proper shuttle plasmid for generation of a pre-viral plasmid comprising multiple open reading frames. For example a trivalent vector may comprise a gag-pol-nef fusion, or possible a "2+1" divalent vaccine comprising, for instance, a gag-pol fusion (*e.g.*, a codon optimized p55 gag and inactivated optimized pol) with each open reading frame being operatively linked to a distinct promoter and transcription termination sequence. Alternatively, the two open reading frames in the same construct may be operatively linked to a single promoter, with the open reading frames operatively linked by an internal ribosome entry sequence (IRES), as disclosed in International Publication No. WO 95/24485, which is hereby incorporated by reference. In the absence of the use of IRES-based technology, it is preferred that a distinct promoter be used to support each respective open reading frame, so as to best preserve vector stability. As examples, and certainly not as limitations, potential multiple transgene vaccines may include a three transgene vector such as that wherein a gagpol fusion and nef gene were included in the same vector with different promoters and termination sequences being used for the gagpol fusion and nef gene. Further, potential "2+1" divalent vaccines of the present invention might be wherein a construct containing gag and nef in the same construct with separate promoters and termination sequences is administered in combination with a construct comprising a pol gene with promoter and termination sequence. Fusion constructs other than the gag-pol fusion described above are also suitable for use in various divalent vaccine strategies and can be composed of any two HIV antigens fused to one another (*e.g.*, nef-pol and gag-nef). These compositions are, as above, preferably delivered along with a viral composition comprising an additional HIV antigen in order to diversify the immune response generated upon inoculation. Therefore, a multivalent vaccine delivered in a single, or possibly second, viral vector is certainly contemplated as part of the present invention. It is important to note, however, that in terms of deciding on an insert for the disclosed viral vectors, due

consideration must be given to the effective packaging limitations of the viral vehicle. Adenovirus, for instance, has been shown to exhibit an upper cloning capacity limit of approximately 105% of the wildtype Ad5 sequence.

Regardless of the gene chosen for expression, it is preferred that the sequence be "optimized" for expression in a mammalian (e.g., human) cellular environment, particularly in the adenoviral constructs. A "triplet" codon of four possible nucleotide bases can exist in 64 variant forms. That these forms provide the message for only 20 different amino acids (as well as transcription initiation and termination) means that some amino acids can be coded for by more than one codon. Indeed, some amino acids have as many as six "redundant", alternative codons while some others have a single, required codon. For reasons not completely understood, alternative codons are not at all uniformly present in the endogenous DNA of differing types of cells and there appears to exist variable natural hierarchy or "preference" for certain codons in certain types of cells. As one example, the amino acid leucine is specified by any of six DNA codons including CTA, CTC, CTG, CTT, TTA, and TTG (which correspond, respectively, to the mRNA codons, CUA, CUC, CUG, CUU, UUA and UUG). Exhaustive analysis of genome codon frequencies for microorganisms has revealed endogenous DNA of *E. coli* most commonly contains the CTG leucine-specifying codon, while the DNA of yeast and slime molds most commonly includes a TTA leucine-specifying codon. In view of this hierarchy, it is generally held that the likelihood of obtaining high levels of expression of a leucine-rich polypeptide by an *E. coli* host will depend to some extent on the frequency of codon use. For example, a gene rich in TTA codons will in all probability be poorly expressed in *E. coli*, whereas a CTG rich gene will probably highly express the polypeptide. Similarly, when yeast cells are the projected transformation host cells for expression of a leucine-rich polypeptide, a preferred codon for use in an inserted DNA would be TTA.

The implications of codon preference phenomena on recombinant DNA techniques are manifest, and the phenomenon may serve to explain many prior failures to achieve high expression levels of exogenous genes in successfully transformed host organisms—a less "preferred" codon may be repeatedly present in the inserted gene and the host cell machinery for expression may not operate as efficiently. This phenomenon suggests that synthetic genes which have been designed to include a projected host cell's preferred codons provide a preferred form of foreign

genetic material for practice of recombinant DNA techniques. Thus, one aspect of this invention is a vaccine administration protocol wherein the recombinant adenoviral vectors (prime and boost vectors) specifically include a gene which is codon optimized for expression in a human cellular environment. As noted herein, a preferred gene for use in the instant invention is a codon-optimized HIV gene and, particularly, HIV gag, pol, env, or nef although, as stated above, the adenoviral vehicles of the instant invention can utilize heterologous nucleic acid which may or may not be codon-optimized. In specific embodiments of the instant invention, the individual can be primed with an adenoviral vector comprising codon-optimized heterologous nucleic acid, and boosted with an adenovirus of an alternative serotype comprising non-codon-optimized nucleic acid. Administration of multiple antigens possesses the possibility for exploiting various different combinations of codon-optimized and non-codon-optimized sequences.

A vaccine composition comprising the recombinant viral vectors either in the priming or boosting dose in accordance with the instant invention may contain physiologically acceptable components, such as buffer, normal saline or phosphate buffered saline, sucrose, other salts and polysorbate. One preferred formulation has: 2.5-10 mM TRIS buffer, preferably about 5 mM TRIS buffer; 25-100 mM NaCl, preferably about 75 mM NaCl; 2.5-10% sucrose, preferably about 5% sucrose; 0.01 -2 mM  $MgCl_2$ ; and 0.001%-0.01% polysorbate 80 (plant derived). The pH should range from about 7.0-9.0, preferably about 8.0. One skilled in the art will appreciate that other conventional vaccine excipients may also be used it make the formulation. The preferred formulation contains 5mM TRIS, 75 mM NaCl, 5% sucrose, 1mM  $MgCl_2$ , 0.005% polysorbate 80 at pH 8.0. This has a pH and divalent cation composition which is near the optimum for Ad5 and Ad6 stability and minimizes the potential for adsorption of virus to a glass surface. It does not cause tissue irritation upon intramuscular injection. It is preferably frozen until use.

The amount of viral particles in the vaccine composition to be introduced into a vaccine recipient will depend on the strength of the transcriptional and translational promoters used and on the immunogenicity of the expressed gene product. In general, an immunologically or prophylactically effective dose of  $1 \times 10^7$  to  $1 \times 10^{12}$  particles and preferably about  $1 \times 10^{10}$  to  $1 \times 10^{11}$  particles is administered directly into muscle tissue. Subcutaneous injection, intradermal introduction, impression through the skin, and other modes of administration such as intraperitoneal, intravenous, or inhalation

delivery are also contemplated. Parenteral administration, such as intravenous, intramuscular, subcutaneous or other means of administration of interleukin-12 protein, concurrently with or subsequent to parenteral introduction of the vaccine compositions of this invention is also advantageous.

5       The administration schemes of the instant invention are based on the priming of the immune response with an adenoviral vehicle of a first serotype comprising a gene encoding an HIV antigen (or antigens) and, following a predetermined length of time, boosting the adenovirus-primed response with an adenoviral vehicle of a second and alternative serotype comprising the gene encoding the HIV antigen(s). Multiple  
10       primings, typically, 1-4, are usually employed, although more may be used. The length of time between prime and boost may typically vary from about four months to a year, but other time frames may be used. The booster dose may be repeated at selected time intervals.

15       A large body of human and animal data supports the importance of cellular immune responses, especially CTL in controlling (or eliminating) HIV infection. In humans, very high levels of CTL develop following primary infection and correlate with the control of viremia. Several small groups of individuals have been described who are repeatedly exposed to HIV but remain uninfected; CTL has been noted in several of these cohorts. In the SIV model of HIV infection, CTL similarly develops  
20       following primary infection, and it has been demonstrated that addition of anti-CD8 monoclonal antibody abrogated this control of infection and leads to disease progression.

25       The following non-limiting Examples are presented to better illustrate the invention.

#### EXAMPLE 1

##### HIV-1 Gag Gene

30       A synthetic gene for HIV gag from HIV-1 strain CAM-1 was constructed using codons frequently used in humans; see Korber *et al.*, 1998 *Human Retroviruses and AIDS*, Los Alamos Nat'l Lab., Los Alamos, New Mexico; and Lathe, R., 1985 *J. Mol. Biol.* 183:1-12. Figure 2 illustrates the nucleotide sequence of the exemplified optimized codon version of full-length p55 gag. The gag gene of HIV-1 strain CAM-1 was selected as it closely resembles the consensus amino acid sequence for the clade

B (North American/European) sequence (Los Alamos HIV database). Advantage of this "codon-optimized" HIV gag gene as a vaccine component has been demonstrated in immunogenicity studies in mice. The "codon-optimized" HIV gag gene was shown to be over 50-fold more potent to induce cellular immunity than the wild type HIV gag gene when delivered as a DNA vaccine.

A KOZAK sequence (GCCACC) was introduced preceding the initiating ATG of the gag gene for optimal expression. The HIV gag fragment with KOZAK sequence was amplified through PCR from V1Jns-HIV gag vector. PVIJnsHIVgag is a plasmid comprising the CMV immediate-early (IE) promoter and intron A, a full-length codon-optimized HIV gag gene, a bovine growth hormone-derived polyadenylation and transcriptional termination sequence, and a minimal pUC backbone; see Montgomery *et al.*, 1993 *DNA Cell Biol.* 12:777-783, for a description of the plasmid backbone.

## EXAMPLE 2

### Generation of Adenoviral Serotype 5 Vector Constructs

#### A. Removal of the Intron A Portion of the hCMV Promoter

GMP grade pVIJnsHIVgag was used as the starting material to amplify the hCMV promoter. The amplification was performed with primers suitably positioned to flank the hCMV promoter. A 5' primer was placed upstream of the *MscI* site of the hCMV promoter and a 3' primer (designed to contain the *BglII* recognition sequence) was placed 3' of the hCMV promoter. The resulting PCR product (using high fidelity *Taq* polymerase) which encompassed the entire hCMV promoter (minus intron A) was cloned into TOPO PCR blunt vector and then removed by double digestion with *MscI* and *BglII*. This fragment was then cloned back into the original GMP grade pVIJnsHIVgag plasmid from which the original promoter, intron A, and the gag gene were removed following *MscI* and *BglII* digestion. This ligation reaction resulted in the construction of a hCMV promoter (minus intron A) + bGHpA expression cassette within the original pVIJnsHIVgag vector backbone. This vector is designated pVIJnsCMV(no intron).

The FLgag gene was excised from pVIJnsHIVgag using *BglII* digestion and the 1,526 bp gene was gel purified and cloned into pVIJnsCMV(no intron) at the *BglII* site. Colonies were screened using *SmaI* restriction enzymes to identify clones that carried the FLgag gene in the correct orientation. This plasmid, designated

pVIJnsCMV(no intron)-FLgag-bGIpA, was fully sequenced to confirm sequence integrity.

B. Construction of the Modified Shuttle Vector -“MRKpdelE1 Shuttle”

- The modifications to the original Ad5 shuttle vector (pdelE1sp1A; a vector comprising Ad5 sequences from base pairs 1-341 and 3524-5798, with a multiple cloning region between nucleotides 341 and 3524 of Ad5, included the following three manipulations carried out in sequential cloning steps as follows:
- (1) The left ITR region was extended to include the *Pac1* site at the junction between the vector backbone and the adenovirus left ITR sequences. This allow for easier manipulations using the bacterial homologous recombination system.
  - (2) The packaging region was extended to include sequences of the wild-type (WT) adenovirus from 342 bp to 450 bp inclusive.
  - (3) The area downstream of pIX was extended 13 nucleotides (i.e., nucleotides 3511-3523 inclusive).
- These modifications (Figure 4) effectively reduced the size of the E1 deletion without overlapping with any part of the E1A/E1B gene present in the transformed PER.C6® cell line. All manipulations were performed by modifying the Ad shuttle vector pdelE1sp1A.

- Once the modifications were made to the shuttle vector, the changes were incorporated into the original Ad5 adenovector backbone pAdHVE3 by bacterial homologous recombination using *E. coli* BJ5183 chemically competent cells.

C. Construction of Modified Adenovector Backbone

- An original adenovector pAdHVE3 (comprising all Ad5 sequences except those nucleotides encompassing the E1 region) was reconstructed so that it would contain the modifications to the E1 region. This was accomplished by digesting the newly modified shuttle vector (MRKpdelE1 shuttle) with *Pac1* and *BstZ1101* and isolating the 2,734 bp fragment which corresponds to the adenovirus sequence. This fragment was co-transformed with DNA from *Clal* linearized pAdHVE3 (E3+adenovector) into *E. coli* BJ5183 competent cells. At least two colonies from the transformation were selected and grown in Terrific™ broth for 6-8 hours until turbidity was reached. DNA was extracted from each cell pellet and then transformed into *E. coli* XL1 competent cells. One colony from the transformation was selected and grown for plasmid DNA purification. The plasmid was analyzed by restriction digestions to identify correct clones. The modified adenovector was designated

MRKpAdHVE3 (E3+ plasmid). Virus from the new adenovector (MRKHVE3) as well as the old version were generated in the PER.C6<sup>®</sup> cell lines. In addition, the multiple cloning site of the original shuttle vector contained ClaI, BamHI, Xho I, EcoRV, HindIII, Sal I, and Bgl II sites. This MCS was replaced with a new MCS containing Not I, Cla I, EcoRV and Asc I sites. This new MCS has been transferred to the MRKpAdHVE3 pre-plasmid along with the modification made to the packaging region and pIX gene.

D. Construction of the new shuttle vector containing modified gag transgene – “MRKpdelE1-CMV(no intron)-FLgag-bGHpA”

The modified plasmid pVIJnsCMV(no intron)-FLgag-bGHpA was digested with *MscI* overnight and then digested with *SfiI* for 2 hours at 50°C. The DNA was then treated with Mungbean nuclease for 30 minutes at 30°C. The DNA mixture was desalted using the Qiaex II kit and then Klenow treated for 30 minutes at 37°C to fully blunt the ends of the transgene fragment. The 2,559 bp transgene fragment was then gel purified. The modified shuttle vector (MRKpdelE1 shuttle) was linearized by digestion with EcoRV, treated with calf intestinal phosphatase and the resulting 6,479 bp fragment was then gel purified. The two purified fragments were then ligated together and several dozen clones were screened to check for insertion of the transgene within the shuttle vector. Diagnostic restriction digestion was performed to identify those clones carrying the transgene in the E1 parallel orientation.

E. Construction of the MRK FG Adenovector

The shuttle vector containing the HIV-1 gag transgene in the E1 parallel orientation, MRKpdelE1-CMV(no intron)-FLgag-bGHpA, was digested with *PacI*. The reaction mixture was digested with *BspZ171*. The 5,291 bp fragment was purified by gel extraction. The MRKpAdHVE3 plasmid was digested with *ClaI* overnight at 37°C and gel purified. About 100 ng of the 5,290 bp shuttle +transgene fragment and ~100 ng of linearized MRKpAdHVE3 DNA were co-transformed into *E. coli* BJ5183 chemically competent cells. Several clones were selected and grown in 2 ml Terrific<sup>™</sup> broth for 6-8 hours, until turbidity was reached. The total DNA from the cell pellet was purified using Qiagen alkaline lysis and phenol chloroform method. The DNA was precipitated with isopropanol and resuspended in 20 µl dH<sub>2</sub>O. A 2 µl aliquot of this DNA was transformed into *E. coli* XL-1 competent cells. A single colony from the transformation was selected and grown overnight in 3 ml LB +100 µg/ml ampicillin. The DNA was isolated using Qiagen columns. A positive clone

was identified by digestion with the restriction enzyme *BstEII* which cleaves within the gag gene as well as the plasmid backbone. The pre-plasmid clone is designated MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA and is 37,498 bp in size.

F. Virus generation of an enhanced adenoviral construct – “MRK Ad5 HIV-1gag”

- 5       MRK-Ad5 HIV-1 gag contains the hCMV(no intron)-FLgag-bGHpA transgene inserted into the new E3+ adenovector backbone, MRKpAdHVE3, in the E1 parallel orientation. We have designated this adenovector MRK Ad5 HIV-1 gag. This construct was prepared as outlined below:

- 10       The pre-plasmid MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA was digested with *PacI* to release the vector backbone and 3.3 µg was transfected by the calcium phosphate method (Amersham Pharmacia Biotech.) in a 6 cm dish containing PER.C6<sup>®</sup> cells at ~60% confluence. Once CPE was reached (7-10 days), the culture was freeze/thawed three times and the cell debris pelleted. 1 ml of this cell lysate was used to infect into a 6 cm dish containing PER.C6<sup>®</sup> cells at 80-90% confluence. Once
- 15       CPE was reached, the culture was freeze/thawed three times and the cell debris pelleted. The cell lysate was then used to infect a 15 cm dish containing PER.C6<sup>®</sup> cells at 80-90% confluence. This infection procedure was continued and expanded at passage 6. The virus was then extracted from the cell pellet by CsCl method. Two bandings were performed (3-gradient CsCl followed by a continuous CsCl gradient).
- 20       Following the second banding, the virus was dialyzed in A105 buffer. Viral DNA was extracted using pronase treatment followed by phenol chloroform. The viral DNA was then digested with *HindIII* and radioactively labeled with [<sup>32</sup>P]dATP. Following gel electrophoresis to separate the digestion products the gel was dried
- 25       down on Whatman paper and then subjected to autoradiography. The digestion products were compared with the digestion products from the pre-plasmid (that had been digested with *PacI/HindIII* prior to labeling). The expected sizes were observed, indicating that the virus had been successfully rescued.

### EXAMPLE 3

- 30       Generation of Adenoviral Serotype 6 Vector Constructs

A. Construction of Ad6 Pre-Adenovirus Plasmid

An Ad6 based pre-adenovirus plasmid which could be used to generate first generation Ad6 vectors was constructed taking advantage of the extensive sequence

homology (approx. 98%) between Ad5 and Ad6. Homologous recombination was used to clone wtAd6 sequences into a bacterial plasmid.

The general strategy used to recover pAd6E1-E3+ as a bacterial plasmid is illustrated in Figure 7. Cotransformation of BJ 5183 bacteria with purified wt Ad6 viral DNA and a second DNA fragment termed the Ad5 ITR cassette resulted in the circularization of the viral genome by homologous recombination. The ITR cassette contains sequences from the right (bp 33798 to 35935) and left (bp 1 to 341 and bp 3525 to 5767) end of the Ad5 genome separated by plasmid sequences containing a bacterial origin of replication and an ampicillin resistance gene. The ITR cassette contains a deletion of E1 sequences from Ad5 342 to 3524. The Ad5 sequences in the ITR cassette provide regions of homology with the purified Ad6 viral DNA in which recombination can occur.

Potential clones were screened by restriction analysis and one clone was selected as pAd6E1-E3+. This clone was then sequenced in its entirety. pAd6E1-E3+ contains Ad5 sequences from bp 1 to 341 and from bp 3525 to 5548, Ad6 bp 5542 to 33784, and Ad5 bp 33967 to 35935 (bp numbers refer to the wt sequence for both Ad5 and Ad6). pAd6E1-E3+ contains the coding sequences for all Ad6 virion structural proteins which constitute its serotype specificity.

#### B. Construction of an Ad6 Pre-Adenovirus Plasmid containing the HIV-1 gag gene (1) Construction of Adenoviral Shuttle Vector:

The shuttle plasmid MRKpdeIE1(Pac/pIX/pack450)+CMVminFL-gag-BGHpA was constructed by inserting a synthetic full-length codon-optimized HIV-1 gag gene into MRKpdeIE1(Pac/pIX/pack450)+CMVmin+BGHpA(str.). MRKpdeIE1(Pac/pIX/pack450)+CMVmin+BGHpA(str.) contains Ad5 sequences from bp 1 to 5792 with a deletion of E1 sequences from bp 451 to 3510. The HCMV promoter and BGH pA were inserted into the E1 deletion in an E1 parallel orientation with a unique BglII site separating them. The synthetic full-length codon-optimized HIV-1 gag gene was obtained from plasmid pV1Jns-HIV-FLgag-opt by BglII digestion, gel purified and ligated into the BglII restriction endonuclease site in MRKpdeIE1(Pac/pIX/pack450)+CMVmin+BGHpA(str.), generating plasmid MRKpdeIE1(Pac/pIX/pack450)+CMVminFL-gag-BGHpA. The genetic structure of MRKpdeIE1(Pac/pIX/pack450)+CMVminFL-gag-BGHpA was verified by PCR, restriction enzyme and DNA sequence analyses.

(2) Construction of pre-adenovirus plasmid:

Shuttle plasmid MRKpdelE1(Pac/pIX/pack450)+CMVminFL-gag-BGHpA was digested with restriction enzymes *PacI* and *BsrI* 107I and then co-transformed into *E. coli* strain BJ5183 with linearized (*ClaI*-digested) adenoviral backbone plasmid, pAd6E1-E3+. The genetic structure of the resulting pMRKAd6gag was verified by restriction enzyme and DNA sequence analysis. The vectors were transformed into competent *E. coli* XL-1 Blue for large-scale production. The recovered plasmid was verified by restriction enzyme digestion and DNA sequence analysis, and by expression of the gag transgene in transient transfection cell culture.

pMRKAd6gag contains Ad5 bp 1 to 450 and from bp 3511 to 5548, Ad6 bp 5542 to 33784, and Ad5 bp 33967 to 35935 (bp numbers refer to the wt sequence for both Ad5 and Ad6). In the plasmid the viral ITRs are joined by plasmid sequences that contain the bacterial origin of replication and an ampicillin resistance gene.

C. Generation of research-grade recombinant MRKAd6gag

To prepare virus for pre-clinical immunogenicity studies, the pre-adenovirus plasmid pMRKAd6gag was rescued as infectious virions in PER.C6<sup>®</sup> adherent monolayer cell culture. To rescue infectious virus, 10 µg of pMRKAd6gag was digested with restriction enzyme *PacI* (New England Biolabs) and transfected into a 6 cm dish of PER.C6<sup>®</sup> cells using the calcium phosphate co-precipitation technique (Cell Pect Transfection Kit, Amersham Pharmacia Biotech Inc.). *PacI* digestion releases the viral genome from plasmid sequences allowing viral replication to occur after entry into PER.C6<sup>®</sup> cells. Infected cells and media were harvested after complete viral cytopathic effect (CPE) was observed. The virus stock was amplified by multiple passages in PER.C6<sup>®</sup> cells. At the final passage virus was purified from the cell pellet by CsCl ultracentrifugation. The identity and purity of the purified virus was confirmed by restriction endonuclease analysis of purified viral DNA and by gag ELISA of culture supernatants from virus infected mammalian cells grown in vitro. For restriction analysis, digested viral DNA was end-labeled with P<sup>33</sup>-dATP, size-fractionated by agarose gel electrophoresis, and visualized by autoradiography.

All viral constructs (adenovirus serotypes 5 and 6) were confirmed for Gag expression by Western blot analysis.

## EXAMPLE 4

Immunization

Rhesus macaques were between 3-10 kg in weight. In all cases, the total dose of each vaccine was suspended in 1 mL of buffer. The macaques were anesthetized (ketamine/xylazine) and the vaccines were delivered intramuscularly ("i.m.") in 0.5-mL aliquots into both deltoid muscles using tuberculin syringes (Becton-Dickinson, Franklin Lakes, NJ). Peripheral blood mononuclear cells (PBMC) were prepared from blood samples collected at several time points during the immunization regimen. All animal care and treatment were in accordance with standards approved by the Institutional Animal Care and Use Committee according to the principles set forth in the *Guide for Care and Use of Laboratory Animals*, Institute of Laboratory Animal Resources, National Research Council.

## EXAMPLE 5

ELISPOT Assay

The IFN- $\gamma$  ELISPOT assays for rhesus macaques were conducted following a previously described protocol (Allen *et al.*, 2001 *J. Virol.* 75(2):738-749), with some modifications. For antigen-specific stimulation, a peptide pool was prepared from 20-amino acid ("aa") peptides that encompass the entire HIV-1 gag sequence with 10-aa overlaps (Synpep Corp., Dublin, CA). To each well, 50  $\mu$ L of  $2-4 \times 10^5$  peripheral blood mononuclear cells (PBMCs) were added. The cells were counted using Beckman Coulter Z2 particle analyzer with a lower size cut-off set at 80 femtoliters ("fL"). Either 50  $\mu$ L of media or the gag peptide pool at 8  $\mu$ g/mL concentration per peptide were added to the PBMC. The samples were incubated at 37°C, 5% CO<sub>2</sub> for 20-24 hrs. Spots were developed accordingly and the plates were processed using custom-built imager and automatic counting subroutine based on the ImagePro platform (Silver Spring, MD). The counts were normalized to  $10^6$  cell input.

## EXAMPLE 6

Anti-p24 ELISA

A modified competitive anti-p24 assay was developed using reagents from the Coulter p24 Antigen Assay kit (Beckman Coulter, Fullerton, CA). Briefly, to a 250- $\mu$ L serum sample, 20  $\mu$ L of Lyse Buffer and 15  $\mu$ L of p24 antigen (9.375 pg) from the Coulter kit were added. After mixing, 200  $\mu$ L of each sample were added to wells

coated with a mouse anti-p24 mAb from the Coulter kit and incubated for 1.5 hr at 37°C. The wells were then washed and 200  $\mu$ L of Biotin Reagent (polyclonal anti-p24-biotin) from the Coulter kit was added to each well. After a 1 hr, 37°C incubation, detection was achieved using streptavidin-conjugated horseradish peroxidase and TMB substrate as described in the Coulter Kit. OD450nm values were recorded. A 7-point standard curve was generated using a serial 2-fold dilution of serum from an HIV-seropositive individual. The lower cut-off for the assay is arbitrarily set at 10 milli Merck units/mL (mMU/mL) defined by a dilution of the seropositive human serum. This cutoff falls at approximately 65% of the maximum bound control signal which corresponds to that obtained with the diluent control only and with no positive analyte.

#### EXAMPLE 7

##### Intracellular Cytokine Staining

To 1 ml of  $2 \times 10^6$  PBMC/mL in complete RPMI media (in 17x100mm round bottom polypropylene tubes (Sarstedt, Newton, NC)), anti-hCD28 (clone L293, Becton-Dickinson) and anti-hCD49d (clone L25, Becton-Dickinson) monoclonal antibodies were added to a final concentration of 1  $\mu$ g/mL. For gag-specific stimulation, 10  $\mu$ L of the peptide pool (at 0.4 mg/mL per peptide) were added. The tubes were incubated at 37 °C for 1 hr., after which 20  $\mu$ L of 5 mg/mL of brefeldin A (Sigma) were added. The cells were incubated for 16 hours at 37 °C, 5% CO<sub>2</sub>, 90% humidity. 4 mL cold PBS/2%FBS were added to each tube and the cells were pelleted for 10 min at 1200 rpm. The cells were re-suspended in PBS/2%FBS and stained (30 min, 4 °C) for surface markers using several fluorescent-tagged mAbs: 20  $\mu$ L per tube anti-hCD3-APC, clone FN-18 (Biosource); 20  $\mu$ L anti-hCD8-PerCP, clone SK1 (Becton Dickinson); and 20  $\mu$ L anti-hCD4-PE, clone SK3 (Becton Dickinson). Sample handling from this stage was conducted in the dark. The cells were washed and incubated in 750  $\mu$ L 1xFACS Perm buffer (Becton Dickinson) for 10 minutes at room temperature. The cells were pelleted and re-suspended in PBS/2%FBS and 0.1  $\mu$ g of FITC-anti-hIFN- $\gamma$ , clone MD-1 (Biosource) was added. After 30 minutes of incubation, the cells were washed and re-suspended in PBS. Samples were analyzed using all four color channels of the Becton Dickinson FACS Calibur instrument. To analyze the data, the low side- and forward-scatter lymphocyte population was initially gated and a common fluorescence cut-off for

cytokine-positive events was used for both CD4<sup>+</sup> and CD8<sup>+</sup> populations, and for both mock and gag-peptide reaction tubes of a sample.

## EXAMPLE 8

### Results

#### A. Immunization Regimen

Cohorts of 3-6 rhesus macaques were immunized following homologous and heterologous prime-boost regimens involving MRKAd5 and MRKAd6 vectors expressing the same codon-optimized HIV-1 gag. The immunization schedule is described in Table 1.

**Table 1.**

Group	Prime	Boost (month 6)
1	10e9 vp MRKAd5-HIVgag at week 0, 4	10e9 vp MRKAd5-HIVgag
2	10e9 vp MRKAd6-HIVgag at week 0, 4	10e9 vp MRKAd6-HIVgag
3	10e9 vp MRKAd5-HIVgag at week 0, 4	10e9 cfu MRKAd6-HIVgag

#### B. T Cell Immune Responses

Vaccine-induced T cell responses against HIV-1 gag were quantified using IFN-gamma ELISPOT assay against a pool of 20-aa peptides that encompassed the entire protein sequence. The results are shown in Figure 5. They are expressed as the number of spot-forming cells (SFC) per million peripheral blood mononuclear cells (PBMCs) that responded to the peptide pool minus the mock control.

The Figure shows the T cell responses induced by two priming immunizations with 10e9 vp MRKAd5-HIVgag followed by a 10e9 vp MRKAd5-HIVgag booster after a long rest (a period of 20-23 weeks; 22 for the MRKAd6-MRKAd6 subjects; 22 for subjects 99D262, 99C117, and 99D227 of the MRKAd5-MRKAd5 group; and 23 for the remaining subjects). Administration of the same dose of MRKAd5 HIV-1 gag at approximately month 6 resulted in slight increases compared to the levels just prior to the boost; the post-boost levels were largely comparable to if not weaker than the peak levels before the boost. This is possibly due to the presence of neutralizing immunity generated against the vector by the first two immunizations. The responses after the boost did not surpass 500 gag-specific T cells per 10e6 PBMC, with a mean of 275 SFC/10e6 PBMC for all 6 monkeys. Similar results were observed when monkeys were given three of 10e9 vp MRKAd6 HIV-1 gag (at 0, 1, 6 months). In two out of the three monkeys, the post-boost levels did not surpass 500 SFC/10e6

- PBMC. In contrast, when both modalities are combined in which animals were given two priming doses of 10<sup>9</sup> vp MRKAd5-HIVgag and a single booster shot of 10<sup>9</sup> pfu MRKAd6-HIVgag, the levels of gag-specific T cells increased to peak responses above 1000 SFC/10<sup>6</sup> PBMC for all 3 monkeys. The ability of MRKAd6-HIVgag to boost effectively MRKAd5-gag-primed immune responses more effectively is possibly due to the presence of neutralizing immunity generated against the MRKAd5 vector by the first two immunizations. The ability of Ad6 to boost primed responses was also evident using a lower priming dose of 10<sup>7</sup> vp of MRKAd5 HIV-1 gag (Figure 6).
- PBMCs from the vaccinees of the heterologous MRKAd5 prime-MRKAd6 boost regimen were analyzed for intracellular IFN- $\gamma$  staining after the priming immunizations (wk 13) and after the booster immunizations (wk 31). The assay provided information on the relative amounts of CD4<sup>+</sup> and CD8<sup>+</sup> gag-specific T cells in the peripheral blood (Table 2). The results indicated that heterologous prime-boost immunization approach was able to elicit in rhesus macaques both HIV-specific CD4+ and CD8+ T cells.

Table 2.

Prime	Boost	ID	Post Prime		Post Boost	
			%CD4+	%CD8+	%CD4+	%CD8+
MRKAd5-HIVgag 10 <sup>9</sup> vp wk 0, 4	MRKAd6-HIVgag 10 <sup>9</sup> pfu wk 27	99C216	0.05	0.21	0.10	1.45
		99C231	0.03	0.10	0.16	1.41
		99C132	0.00	0.02	0.04	0.15

- Numbers reflect the percentages of circulating CD3+ lymphocytes that are either gag-specific CD4+ or gag-specific CD8+ cells. Mocks values have been subtracted.  
 \*No detectable antigen-specific CD4+ T cells above background  
 \*\*Collected at wk 35 instead of wk 31

### C. Humoral Immune Responses

- The p24-specific antibody titers were determined for each animal at several time points. The geometric mean titers for each cohort were calculated and shown in Figure 10. Two doses of MRKAd5 HIV-1 gag or MRKAd6 HIV-1 gag were able to induce moderate levels of anti-p24 antibodies (about 1000 mMU/mL).
- Administration of the same viral vector booster resulted in 5-10 fold increase in the humoral immune responses. Boosting MRKAd5 HIV-1 gag primed monkeys with MRKAd6-gag resulted in a comparable in antibody levels. Boosting with the same virus can have its limitations, though, as the effect can be negatively impacted by any

significant neutralizing Ad5-specific activity. The booster effect of a non-matched Ad serotype, by contrast, would not be affected by any pre-existing neutralizing titers directed at Ad5.

## 5 EXAMPLE 9

### Generation of a Completely Adenoviral Serotype 6 Vector Construct

#### A. Construction of a Completely Ad6 Pre-Adenovirus Plasmid

An Ad6 based pre-adenovirus plasmid derived from Ad6 sequence and not constructed taking advantage of the homology between Ad5 and Ad6 can be  
10 generated and used to generate first generation Ad6 vectors. Homologous recombination is used to clone wtAd6 sequences into a bacterial plasmid.

The general strategy used to recover such a pMRKAd6E1- bacterial plasmid is illustrated in Figure 13. Basically, cotransformation of BJ 5183 bacteria with purified wt Ad6 viral DNA and a second DNA fragment termed the Ad6 ITR cassette would  
15 effectuate circularization of the viral genome by homologous recombination. The ITR cassette contains sequences from the right (bp 35460 to 35759) and left (bp 1 to 450 and bp 3508 to 3807) end of the Ad6 genome separated by plasmid sequences containing a bacterial origin of replication and an ampicillin resistance gene. These three segments were generated by PCR and cloned sequentially into pNEB193 (a  
20 commonly used commercially available cloning plasmid (New England Biolabs cat# N3051S) containing a bacterial origin of replication ,ampicillin resistance gene and a multiple cloning site into which the PCR products are introduced), generating pNEBAd6-3 (the ITR cassette). The ITR cassette contains a deletion of E1 sequences from Ad5 451 to 3507. The Ad6 sequences in the ITR cassette provide regions of  
25 homology with the purified Ad6 viral DNA in which recombination can occur.

PMRKAd6E1- can then be used to generate first generation Ad6 vectors containing transgenes in E1 as described in the previous example.

## 30 EXAMPLE 10

### In Vivo Immunogenicity

#### A. Immunization

Rhesus macaques were between 3-10 kg in weight. In all cases, the total dose of each vaccine was suspended in 1 mL of buffer. The macaques were anesthetized

(ketamine/xylazine) and the vaccines were delivered i.m. in 0.5-mL aliquots into both deltoid muscles using tuberculin syringes (Becton-Dickinson, Franklin Lakes, NJ). Peripheral blood mononuclear cells (PBMC) were prepared from blood samples collected at several time points during the immunization regimen. All animal care and treatment were in accordance with standards approved by the Institutional Animal Care and Use Committee according to the principles set forth in the *Guide for Care and Use of Laboratory Animals*, Institute of Laboratory Animal Resources, National Research Council.

#### B. ELISPOT Assay

The IFN- $\gamma$  ELISPOT assays for rhesus macaques were conducted following a previously described protocol (Allen et al., 2001 *J. Virol.* 75(2): 738-749), with some modifications. For antigen-specific stimulation, a peptide pool was prepared from 20-aa peptides that encompass the entire HIV-1 gag sequence with 10-aa overlaps (Synpep Corp., Dublin, CA). To each well, 50  $\mu$ L of  $2-4 \times 10^5$  peripheral blood mononuclear cells (PBMCs) were added; the cells were counted using Beckman Coulter Z2 particle analyzer with a lower size cut-off set at 80 fL. Either 50  $\mu$ L of media or the gag peptide pool at 8  $\mu$ g/mL concentration per peptide were added to the PBMC. The samples were incubated at 37°C, 5% CO<sub>2</sub> for 20-24 hrs. Spots were developed accordingly and the plates were processed using custom-built imager and automatic counting subroutine based on the ImagePro platform (Silver Spring, MD); the counts were normalized to  $10^6$  cell input.

#### C. Results

Rare Serotype Vaccine Vector as a Heterologous Booster. A cohort of three rhesus macaques was immunized initially with 3 doses (wk 0, 4, 16) of  $10^8$  vp of MRKAd5-gag. At wk 59, the animals received a booster vaccine of  $10^{10}$  vp Ad35 $\Delta$ E1gag $\Delta$ E4Ad5Orf6 (an Ad35 virus engineered to contain an E1 deletion (from Ad35 bps 457-3402); and a deletion of E4 Orf6 (from Ad35 bps 31912-34418) substituted with Ad5 Orf6). A separate cohort of naïve animals received a single dose of the booster vaccine. The results of the IFN- $\gamma$  ELISPOT analyses of PBMC collected during the course of the studies are shown in Table 3.

Table 3.

Animal	Prime (Wk 0, 4, 16)	Boost (Wk 59)	Pre		Prime <sup>b</sup>		Pre-Boost <sup>c</sup>		Post-Boost <sup>d</sup>	
			Mock <sup>e</sup>	Gag <sup>f</sup>	Mock	Gag	Mock	Gag	Mock	Gag
Monkey 11	10 <sup>8</sup> vp MFKAd5-gag	10 <sup>8</sup> vp Ad35AE1gagAE4Ad5ON6	0	1	1	153	0	25	3	1120
Monkey 12	10 <sup>8</sup> vp MFKAd5-gag	10 <sup>8</sup> vp Ad35AE1gagAE4Ad5ON6	4	5	3	269	0	23	1	659
Monkey 13	10 <sup>8</sup> vp MFKAd5-gag	10 <sup>8</sup> vp Ad35AE1gagAE4Ad5ON6	1	3	3	150	0	10	1	489
Monkey 14	none	10 <sup>8</sup> vp AG35AE1gagAE4Ad5ON6	1	9	ND <sup>g</sup>	ND	ND	ND	0	20
Monkey 15	none	10 <sup>8</sup> vp AG35AE1gagAE4Ad5ON6	3	3	ND	ND	ND	ND	1	81
Monkey 16	none	10 <sup>8</sup> vp AG35AE1gagAE4Ad5ON6	0	6	ND	ND	ND	ND	0	48

<sup>a</sup>Mock, no peptide; gag, 20-mer peptide pool encompassing entire gag sequence<sup>b</sup>Peak response after 2 or 3 doses of the priming vaccine<sup>c</sup>Wk 59<sup>d</sup>4 wks after boost<sup>e</sup>ND, not determined

5 It is apparent that Ad35-based HIV vectors can be utilized to amplify

10 the existing pools of HIV-specific T cells. The increases in the levels of gag-specific T cells from the pre-boost levels to those measured at 4 wks post boost were consistently larger than the levels induced by the same booster vaccine in naïve animals.

## WHAT IS CLAIMED IS:

1. A method for inducing an enhanced immunological response against an HIV-1 antigen in a mammalian host, said method comprising the steps of:
  - 5 (a) inoculating the mammalian host with a recombinant adenoviral vector of a first serotype which is at least partially deleted in E1 and devoid of E1 activity comprising a gene encoding an HIV-1 antigen or immunologically relevant modification thereof; and thereafter
  - (b) inoculating the mammalian host with a boosting immunization comprising  
10 a recombinant adenoviral vector of a second serotype which is at least partially deleted in E1 and devoid of E1 activity comprising a gene encoding the HIV-1 antigen or immunologically relevant modification thereof.
2. A method in accordance with claim 1 wherein the HIV-1 antigen is HIV-1 gag.
- 15 3. A method in accordance with claim 1 wherein the HIV-1 antigen is HIV-1 nef.
4. A method in accordance with claim 1 wherein the HIV-1 antigen is HIV-1 pol.
5. A method in accordance with claim 1 wherein at least one gene  
20 encoding the HIV-1 antigen or immunologically relevant modification thereof comprises codons optimized for expression in a mammalian host.

6. A method in accordance with claim 1 wherein one or more of the recombinant adenoviral vectors comprise a gene expression cassette, said gene expression cassette which comprises:

- (a) a nucleic acid encoding an HIV-1 antigen;
- 5 (b) a heterologous promoter operatively linked to the nucleic acid encoding the antigen; and
- (c) a transcription termination sequence.

7. A method in accordance with claim 6 wherein the gene expression cassette in at least one of the recombinant adenoviral vectors is inserted into the E1  
10 region.

8. A method in accordance with claim 6 wherein the promoter is an immediate early human cytomegalovirus promoter.

9. A method in accordance with claim 6 wherein the transcription termination sequence is a bovine growth hormone polyadenylation and transcription  
15 termination sequence.

10. A method for inducing an enhanced immunological response against an HIV-1 antigen in a mammalian host, said method comprising the steps of:

- (a) inoculating the mammalian host with a recombinant adenoviral vector of serotype 5 at least partially deleted in E1 and devoid of E1 activity comprising a gene  
20 encoding an HIV-1 antigen or immunologically relevant modification thereof; and thereafter

- (b) inoculating the mammalian host with a boosting immunization comprising a recombinant adenoviral vector of serotype 6 at least partially deleted in E1 and

devoid of E1 activity comprising a gene encoding the HIV-1 antigen or immunologically relevant modification thereof.

11. A method in accordance with claim 10 wherein the recombinant adenoviral vector of step (a) is deleted of base pairs 451-3510.
- 5 12. A method in accordance with claim 10 wherein the recombinant adenoviral vector of step (b) is deleted of base pairs 451-3507.
13. A method in accordance with claim 10 wherein at least one gene encoding the HIV-1 antigen or immunologically relevant modification thereof comprises codons optimized for expression in a mammalian host.
- 10 14. A method in accordance with claim 10 wherein the HIV-1 antigen is HIV-1 gag.
15. A method in accordance with claim 10 wherein the HIV-1 antigen is HIV-1 nef.
16. A method in accordance with claim 10 wherein the HIV-1 antigen is  
15 HIV-1 pol.
17. A method in accordance with claim 10 wherein one or more of the recombinant adenoviral vectors comprise a gene expression cassette, said gene expression cassette which comprises:
  - (a) a nucleic acid encoding an HIV-1 antigen;
  - 20 (b) a heterologous promoter operatively linked to the nucleic acid encoding the antigen; and
  - (c) a transcription termination sequence.

18. A method in accordance with claim 17 wherein the gene expression cassette in at least one of the recombinant adenoviral vectors is inserted into the E1 region.

19. A method in accordance with claim 17 wherein the promoter is an immediate early human cytomegalovirus promoter.

20. A method in accordance with claim 17 wherein the transcription termination sequence is a bovine growth hormone polyadenylation and transcription termination sequence.

21. A method for inducing an enhanced immunological response against an HIV-1 gag antigen in a mammalian host, said method comprising the steps of:

(a) inoculating the mammalian host with a recombinant adenoviral vector of serotype 5 at least partially deleted in E1 and devoid of E1 activity comprising a gene encoding an HIV-1 gag antigen or immunologically relevant modification thereof; and thereafter

(b) inoculating the mammalian host with a boosting immunization comprising a recombinant adenoviral vector of serotype 6 at least partially deleted in E1 and devoid of E1 activity comprising a gene encoding the HIV-1 gag antigen or immunologically relevant modification thereof.

22. A method for inducing an enhanced immunological response against an HIV-1 antigen in a mammalian host, said method comprising the steps of:

(a) inoculating the mammalian host with a recombinant adenoviral vector of serotype 5 at least partially deleted in E1 and devoid of E1 activity comprising a gene

encoding an HIV-1 antigen or immunologically relevant modification thereof; and thereafter

- (b) inoculating the mammalian host with a boosting immunization comprising a recombinant adenoviral vector of serotype 35 at least partially deleted in E1 and devoid of E1 activity comprising a gene encoding the HIV-1 antigen or immunologically relevant modification thereof.

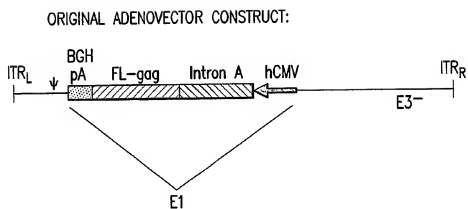
23. A method in accordance with claim 22 wherein at least one gene encoding the HIV-1 antigen or immunologically relevant modification thereof comprises codons optimized for expression in a mammalian host.
- 10 24. A method in accordance with claim 22 wherein the HIV-1 antigen is HIV-1 gag.
25. A method in accordance with claim 22 wherein the HIV-1 antigen is HIV-1 nef.
26. A method in accordance with claim 22 wherein the HIV-1 antigen is HIV-1 pol.
- 15 27. A method in accordance with claim 22 wherein one or more of the recombinant adenoviral vectors comprise a gene expression cassette, said gene expression cassette which comprises:
- (a) a nucleic acid encoding an HIV-1 antigen;
- 20 (b) a heterologous promoter operatively linked to the nucleic acid encoding the antigen; and
- (c) a transcription termination sequence.

28. A method in accordance with claim 27 wherein the gene expression cassette in at least one of the recombinant adenoviral vectors is inserted into the E1 region.

29. A method in accordance with claim 27 wherein the promoter is an  
5 immediate early human cytomegalovirus promoter.

30. A method in accordance with claim 27 wherein the transcription termination sequence is a bovine growth hormone polyadenylation and transcription termination sequence.

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ORIGINAL HIV-1 gag ADENOVECTOR.

FIG. 1

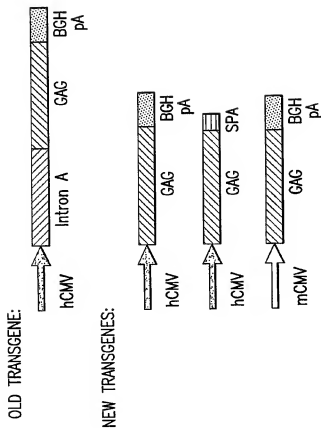
2/70

Sequence of the open reading frame for FL-gag (human codon optimized)

atgggtgctagggcttctgtgtgtgtgtgagctggacaagtgggagaagatcaggctgaggcctgggtgg  
 caagaagaagtacaagctaaagcacattgtgtggcctccaggagctggagaggtttgtgtgaacctggc  
 ctgtcggagacctctgaggggtgcaggcagatcctgggcccagctccagccctccctgcaaacaggctctgagg  
 agctgaggctccctgtacaacacagtggctaccctgtactgtgtgcaccagaagattgatgtgaaggacaccaag  
 gaggccctggagaagattgaggaggagcagaacaagtccaagaagaaggcccagcaggctgctgtgtggtc  
 acaggcaactccagccagggtgtccagaactaccctattgtgcagaacctccaggccagatggtgcaccag  
 gccatctccccccggacctgaatgcctgggtgaaggtggtggaggagaaggccttctcccttgaggatccc  
 catgttctctgcccctgtctgaggggtgccacccccaggacctgaacaccatgctgaacacagtggggggccatc  
 aggctgccatgcagatgctgaaggagaccatcaatgaggaggctgctgagtgggacaggctgcatcctgtgc  
 acgtggccccattgccccggccagatgagggagcccagggtctgtgacattgtctggcaccacctccacct  
 ccaggagcagattggctggatgaccaacaaccccccatcctgtggggaaatctacaagagtggtatcat  
 cctgggacctgaacaagattgtgaggatgtactccccacacctccatcctggacatcaggcaggggcccaaggag  
 ccttcagggactatgtggacaggttctacaagacctgagggtgagcaggcctcccaggaggtgaagaact  
 ggatgcagagacctgtggtgcagaatgccaaacctgactgcaagaccatcctgaaggccctggggccctg  
 ctgccacctggaggagatgatgacagcctgccaggggtggggggccctggtcacaggccagggtgctg  
 gctgaggccatgtcccagtgaccaactccgccaccatcatgatgcagaggggcaacttcaggaaaccagag  
 gaagacagtgaaagtgttcaactgtggcaaggtgggccacattgccagaactgtaggggccccagggaaga  
 agggctgctggaagtgtggcaaggggggccaccagatgaaggactgcaatgagagggcaggccaacttccgt  
 ggcaaaatctggccctcccaagggcaggcctggcaacttctccagtcaggcctgagccccagagccct  
 cccgaggagtccttcaggtttggggaggagaagaccaccccgagccagaagcaggagccattgacaagg  
 agctgtacccccctggctccctgaggctccctgtttggcaacgacccctcctccagtaaaataaagccgggca  
 gat

FIG.2

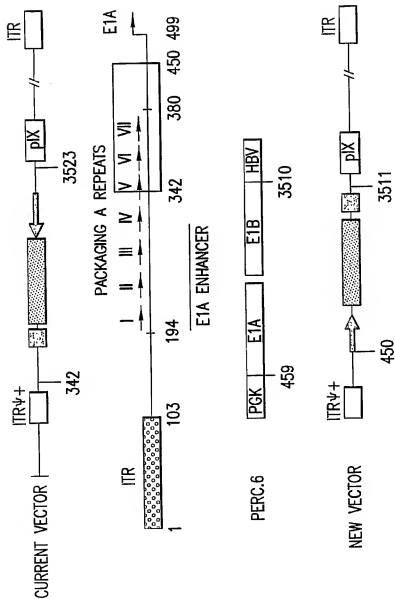
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DIAGRAMMATIC REPRESENTATION OF THE ORIGINAL HIV-1 GAG TRANSGENE AND THE SERIES OF NEW TRANSGENE CONSTRUCTIONS.

FIG.3

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MODIFICATIONS MADE TO THE CURRENT ADENOVECTOR BACKBONE IN THE GENERATION OF THE NEW VECTOR.

FIG.4

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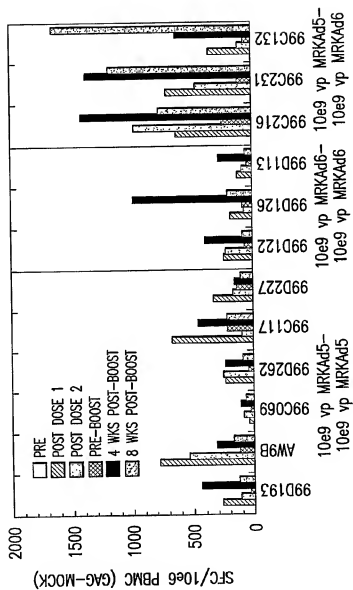


FIG. 5

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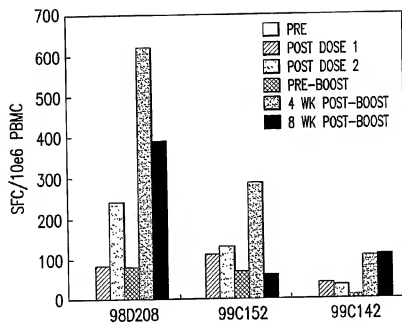


FIG.6

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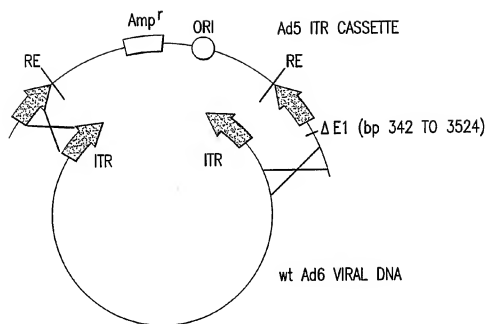


FIG.7

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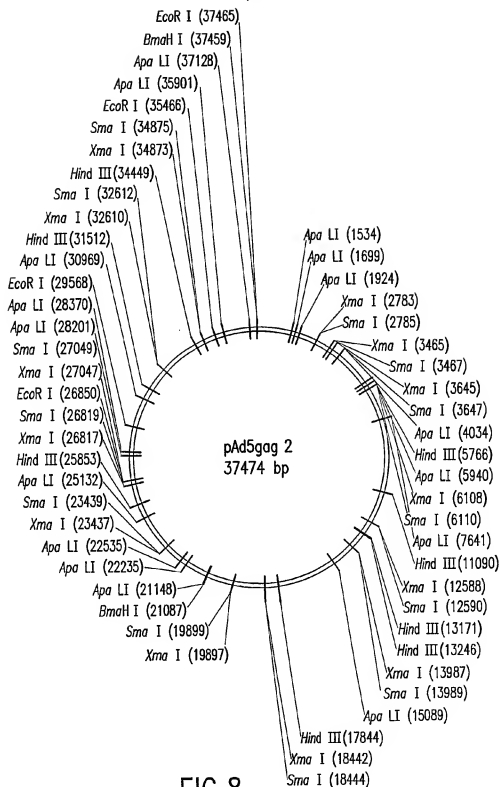


FIG.8

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PacI

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1  TTCTTAATTA ACATCATCAA TAATATACCT TATTTTGGAT TGAAGCCAAT
   AAGAATTAAT TGTAGTAGTT ATTATATGGA ATAAAACTTA ACTTCGGTTA

51  ATGATAATGA GGGGGTGGAG TTTGTGACGT GCGCGGGGCG GTGGGAACGG
   TACTATTACT CCCCCACCTC AAACACTGCA CCGCGCCCGC CACCCTTGCC

101  GCGGGGTGAC GTAGTAGTGT GCGGGAAGTG TGATGTTGCA AGTGTGCGGC
   CCGCCCACTG CATCATCACA CCGCCTTCAC ACTACAACGT TCACACCGCC

151  AACACATGTA AGCGACGGAT GTGGCAAAAG TGACGTTTTT GGTGTGCGCC
   TTGTGTACAT TCGCTGCCTA CACCGTTTTT CTGCAAAAA CCACACGCGG

201  GGTGTACACA GGAAGTGACA ATTTTCGCGC GGTTTTAGGC GGTGTTGTGA
   CCACATGTGT CCTTCACTGT TAAAAGCGCG CCAAAATCCG CCTACAACAT

251  GTAAATTTGG GCGTAACCGA GTAAGATTG GCCATTTTCG CGGGAAGT
   CTTTAAACC CGCATTGGCT CATTCTAAAC CGGTAAAGC GCCCTTTTGA

301  GAATAAGAGG AAGTGAAATC TGAATAATTT TGTGTTACTC ATAGCGCGTA
   CTTATTTCCT TTCACTTTAG ACTTATTAAA ACACATGAG TATCGCGCAT

351  ATATTTGTCT AGGGCGCGCG GGACTTTGAC CGTTTACGTG GAGACTCGCC
   TATAACAGA TCCCGGCGCC CCGTAAACG CCAATGCGC CTCTGAGCGG

401  CAGGTGTTTT TCTCAGGTGT TTTCCGCGTT CCGGGTCAAA GTTGCGTTTT
   GTCCACAAAA AGAGTCCACA AAAGGCGCAA GGCCAGTTT CAACCGCAAA

451  TATTATTATA GCGCGCGCGC ATCCATTGCA TACGTTGTAT CCATATCAT
   ATAATAATAT CCGCGGCGCG TAGGTAACGT ATGCAACATA GGTATAGTAT

501  ATATGTACAT TTATATTGGC TCATGTCCAA CATTACCGCC ATGTTGACAT
   TATACATGTA AATATAACCG AGTACAGGTT GTAATGCGCG TACAACGTGA

551  TGATTATTGA CTAGTTATTA ATAGTAATCA ATTACGGGGT CATTAGTTCA
   ACTAATAACT GATCAATAAT TATCATTAGT TAATGCCCCA GTAATCAAGT

601  TAGCCCATAT ATGGAGTTCC GCGTTACATA ACTTACGGTA AATGGCCCGC
   ATCGGGTATA TACCTCAAGG CGCAATGTAT TGAATGCCAT TTACCGGGCG

651  CTGGCTGACC GCCAACGAC CCCCGCCAT TGACGTCAAT AATGACGTAT
   GACGACTGGC CGGGTTGCTG GGGGCGGGTA ACTGCAGTTA TTACTGCATA

701  GTTCCCATAG TAACGCCAAT AGGGACTTTC CATTGACGTC AATGGGTGGA
   CAAGGGTATC ATTGCGGTTA TCCCTGAAAG GTAACGCGAG TTACCCACCT

751  GTATTTACGG TAAACTGCC ACTTGGCAGT ACATCAAGTG TATCATATGC
   CATAAATGCC ATTTGACGGG TGAACGTC AATGATGTC ATAGTATACG

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FIG.9A-1

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801 CAAGTACGCC CCCTATTGAC GTCAATGACG GTAAATGGCC CGCCTGGCAT  
 GTTCATGCGG GGGATAACTG CAGTTACTGC CATTTACCGG GCGGACCGTA  
 851 TATGCCCAGT ACATGACCTT ATGGGACTTT CCTACTTGGC AGTACATCTA  
 ATACGGGTCA TGTACTGGAA TACCCTGAAA GGATGAACCG TCATGTAGAT  
 901 CGTATTAGTC ATCGCTATTA CCATGGTGAT GCGGTTTTGG CAGTACATCA  
 GCATAATCAG TAGCGATAAT GGTACCACTA CGCCAAAACC GTCATGTAGT  
 951 ATGGGCGTGG ATAGCGGTTT GACTCACGGG GATTTCACAG TCTCCACCCC  
 TACCCGCACC TATCGCCAAA CTGAGTGCCC CTAAGGTTT AGAGGTGGGG  
 1001 ATTGACGTCA ATGGGAGTTT GTTTTGGCAC AAAATCAAC GGGACTTTCC  
 TAACTGCAGT TACCCTCAAA CAAACCGTG GTTTAGTTG CCCTGAAAGG  
 1051 AAAATGTCGT AACAACTCCG CCCCATTGAC GCAAATGGGC GGTAGGCGTG  
 TTTTACAGCA TTGTTGAGGC GGGGTAAC TGTTTACCG CCATCCGCAC  
 1101 TACGGTGGGA GGTCTATATA AGCAGAGCTC GTTTAGTGAA CCGTCAGATC  
 ATGCCACCCT CCAGATATAT TCGTCTCGAG CAAATCACTT GGCAGTCTAG  
 1151 GCCTGGAGAC GCCATCCACG CTGTTTTGAC CTCCATAGAA GACACCGGGA  
 CGGACCTCTG CGGTAGGTGC GACAAAAC TGAGGTATCTT CTGTGGCCCT  
 1201 CCGATCCAGC CTCGCGGGCC GGAACGGTG CATTGGAACG CGGATCCCCC  
 GGCTAGGTCG GAGGCGCGG CCCTTGCCAC GTAACCTTGC GCCTAAGGGG  
 1251 GTGCCAAGAG TGAGATCTAC CATGGGTGCT AGGGCTTCTG TGCTGTCTGG  
 CACGGTTCTC ACTCTAGATG GTACCCACGA TCCCGAAGAC ACGACAGACC  
 1301 TGGTGAGCTG GACAAGTGGG AGAAGATCAG GCTGAGGCCT GGTGGCAAGA  
 ACCACTCGAC CTGTTCAACC TCTTCTAGTC CGACTCCGGA CCACCGTTCT  
 1351 AGAAGTACAA GCTAAGCAC ATTGTGTGGG CCTCCAGGGA GCTGGAGAGG  
 TCTTCATGTT CGATTTCTG TAACACACC GAGGAGTCCT CGACCTCTCC  
 1401 TTTGCTGTGA ACCCTGGCCT GCTGGAGACC TCTGAGGGGT CGAGGCAGAT  
 AAACGACACT TGGGACCGGA CGACCTCTGG AGACTCCCCA CGTCCGTCTA  
 1451 CCTGGGCCAG CTCCAGCCCT CCCTGCAAC AGGCTCTGAG GAGCTGAGGT  
 GGACCCGGTC GAGGTGCGGA GGGACGTTTG TCCGAGACTC CTCGACTCCA  
 1501 CCCTGTACAA CACAGTGGCT ACCCTGTACT GTGTGCACCA GAAGATTGAT  
 GGGACATGTT GTGTACCCGA TGGGACATGA CACACGTGGT CTTCTAACTA  
 1551 GTGAAGGACA CCAAGGAGGC CCTGGAGAAG ATTGAGGAGG AGCAGAACAA  
 CACTTCCTGT GGTTCCTCCG GGACCTCTTC TAACTCTCC TCGCTTGTGT  
 1601 GTCCAAGAAG AAGGCCCAGC AGGCTGCTGC TGGCACAGGC AACTCCAGCC  
 CAGGTTCTTC TTCCGGGTGC ACCGTGTCCG TTGAGGTCGG

FIG.9A-2

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1651 AGGTGTCCCA GAACTACCCC ATTGTGCAGA ACCTCCAGGG CCAGATGGTG  
 TCCACAGGGT CTTGATGGGG TAACACGTCT TGGAGGTCCC GGTCATCCAC  
 1701 CACCAGGCCA TCTCCCCCG GACCTGAAT GCCTGGGTGA AGGTGGTGGA  
 GTGGTCCGGT AGAGGGGGGC CTGGGACTTA CGGACCCACT TCCACCACCT  
 1751 GGAGAAGGCC TTCTCCCTG AGGTGATCCC CATGTTCTCT GCCCTGTCTG  
 CCTCTCCGG AAGAGGGGAC TCCACTAGGG GTACAAGAGA CGGACAGAC  
 1801 AGGGTGCCAC CCCCCAGGAC CTGAACACCA TGCTGAACAC AGTGGGGGGC  
 TCCACGGTG GGGGTCCTG GACTTGTGTG ACGACTTGTG TCACCCCCCG  
 1851 CATCAGGCTG CCATGCAGAT GCTGAAGSAG ACCATCAATG AGGAGGCTGC  
 GTAGTCCGAC GGTACGTCTA CGACTTCCTC TGGTAGTTAC TCCTCCGACG  
 1901 TGAGTGGGAC AGGCTGCATC CTGTGCACGC TGGCCCCATT GCCCCGGCC  
 ACTCACCTCT TCCGACGTAG GACACGTGCG ACCGGGGTAA CGGGGCCGG  
 1951 AGATGAGGGA GCCCAGGGG TCTGACATTG CTGGCACCAC TCACCACCTC  
 TCTACTCCT CGGGTCCCCG AACTGTAAAC GACCGTGGTG GAGGTGGGAG  
 2001 CAGGAGCAGA TTGGCTGGAT GACCAACAAC CCCCCATCC CTGTGGGGGA  
 GTCTCTGTCT AACCGACCTA CTGGTTGTTG GGGGGGTAGG GACACCCCT  
 2051 AATCTACAAG AGGTGGATCA TCCTGGGCTT GAACAAGATT GTGAGGATGT  
 TTAGATGTTT TCCACCTAGT AGSACCCGGA CTGTCTTAA CACTCCTACA  
 2101 ACTCCCCAC CTCCATCCTG GACATCAGGC AGGGCCCCAA GGAGCCCTTC  
 TGAGGGGGTG GAGGTAGGAC CTGTAGTCCG TCCCGGGGTT CCTCGGGAAG  
 2151 AGGGACTATG TGGACAGGTT CTACAAGACC CTGAGGGCTG AGCAGGCTC  
 TCCCTGATAC ACCTGTCCAA GATGTTCTGG GACTCCCGAC TCGTCCGGAG  
 2201 CCAGGAGGTG AAGAACTGGA TGACAGAGAC CCTGCTGGTG CAGAATGCCA  
 GGTCTCCAC TTCTTGACCT ACTGTCTCTG GAGCAGCCAC GTCTTACGGT  
 2251 ACCCTGACTG CAAGACCATC CTGAAGGCC TGGGCCCTGC TGCCACCCTG  
 TGGGACTGAC GTTCTGGTAG GACTTCCGGG ACCCGGGACG ACGGTGGGAC  
 2301 GAGGAGATGA TGACAGCCTG CCAGGGGGTG GGGGGCCCTG GTCACAAGGC  
 CTCTCTACT ACTGTCCGAC GGTCCCCAC CCCCCGGGAC CAGTGTCCG  
 2351 CAGGGTGCTG GCTGAGGCCA TGTCCCAGGT GACCAACTCC GCCACCATCA  
 GTCCACGAC CGACTCCGGT ACAGGGTCCA CTGGTTGAGG CGGTGGTAGT  
 2401 TGATGCAGAG GGGCAACTTC AGGAACACAGA GGAAGACAGT GAAGTGCTTC  
 ACTACGTCTC CCGTTGAAG TCCTTGTGCT CCTTCTGTCA CTTACAGGAG  
 2451 AACTGTGGCA AGGTGGGCCA CATTGCCAAG AACTGTAGGG CCCCCAGSAA  
 TTGACACCGT TCCACCCGGT GTAACGGTTC TTGACATCCC GGGGTCCTT

FIG.9A-3

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2501 GAAGGGCTGC TGGAAAGTGT GCAAGGAGGG CCACCAGATG AAGGACTGCA  
 CTTCCCGACG ACCTTCACAC CGTTCTCCG GGTGGTCTAC TTCTGACGT

2551 ATGAGAGGCA GGCCAACCTC CTGGGCAAAA TCTGGCCTC CCACAAGGGC  
 TACTCTCCGT CCGGTTGAAG GACCCGTTTT AGACCGGGAG GGTGTTCCCG

2601 AGGCCTGGCA ACTTCTCCCA GTCCAGGCCT GAGCCACAG CCCCTCCGGA  
 TCCGGACCGT TGAAGGAGGT CAGGTCGGA CTCGGGTGTC GGGGAGGGCT

2651 GGAGTCCCTC AGGTTTGGGG AGGAGAAGAC CACCCCAAGC CAGAAGCAGG  
 CCTCAGGAAG TCCAAACCC TCCTCTCTG GTGGGGGTG CTCTTCGTCC

2701 AGCCCATTTGA CAAGGAGCTG TACCCCTGG CCTCCCTGAG GTCCTGTGT  
 TCGGGTAACT GTTCTCTGAC ATGGGGGACC GGAGGGACTC CAGGGACAAA

2751 GGCAACGACC CCTCTCCCA GTAAATAAA GCCCGGGCAG ATCTGCTGTG  
 CCGTTGCTGG GGAGGAGGGT CATTTTATTT CGGCCCGTC TAGACGACAC

2801 CCTTCTAGTT GCCAGCCATC TGTGTTTGC CCTCCCCCG TGCCCTTCCTT  
 GGAAGATCAA CGGTCCGTAG ACAACAACG GGGAGGGGGC ACGGAAGGAA

2851 GACCTGGAA GGTGCCACTC CCACTGTCCT TTCTAATAA AATGAGGAAA  
 CTGGGACCTT CCACGGTGAG GGTGACAGGA AAGGATTATT TTACTCCTTT

2901 TTGCATCGCA TTGTCTGAGT AGGTGTCAAT CTATTCTGG GGTGGGGTG  
 AACGTAGCGT AACAGACTCA TCCACAGTAA GATAAGACCC CCCACCCAC

2951 GGGCAGGACA GCAAGGGGGA GGATTGGGAA GACAATAGCA GGCATGCTGG  
 CCGTCTCTGT CGTCCCCCT CTAACCCCT CTGTTATCGT CCGTACGACC

3001 GGATGCGGTG GGCTCTATGG CCGATCGGCG CGCCGTAAGT AAATGTGTGG  
 CCTACGCCAC CCGAGATACC GGCTAGCCGC GCGGCATGAC TTACACACC

3051 GCGTGGCTTA AGGGTGGGAA AGAATATATA AGGTGGGGGT CTTATGTAGT  
 CGCACCGAAT TCCCACCCCT TCTATATAT TCCACCCCA GAATACATCA

3101 TTTGTATCTG TTTTGCAGCA GCCGCCGCCG CCATGAGCAC CAACTGTTT  
 AAACATAGAC AAAACGTCTG CGCGGCGGCG GGTACTCGTG GTTGAGCAAA

3151 GATGGAAGCA TTGTGAGTC ATATTGACA ACGCGCATGC CCCCATGGG  
 CTACCTTCTG AACACTGAG TATAAACTGT TGCCTGACG GGGGTACCCG

3201 CGGGGTGCGT CAGAAATGTA TGGGCTCCAG CATTGATGGT GCGCCGTC  
 GCCCCACGCA GTCTTACACT ACCCGAGGTC GTAACACCA GCGGGGAGG

3251 TGCCCCGAAA CTCTACTACC TTGACATACG AGACCGTGTC TGAACCGCCG  
 ACGGGCGTTT GAGATGATGG AACTGATGTC TCTGGCACAG ACCTTGCGGG

3301 TTGGAGACTG CAGCCTCCGC CGCCGCTTCA GCGCTGACG CCACCGCGCG  
 AACCTCTGAC GTCGGAGGCG GCGCGAAGT CCGCGACGTC GGTGGCGGGC

FIG.9A-4

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3351 CGGGATTGTG ACTGACITTTG CTTTCCTGAG CCCGCTTGCA AACAGTGCAG  
 GCCCTAACAC TGA CTGAAAC GAAAGGACTC GGGCGAACGT TTGTACAGTC  
 3401 CTTCCCGTTC ATCCGCCCGC GATGACAAGT TGACGGCTCT TTTGGCACAA  
 GAAGGGCAAG TAGCGGGCG CTA CTGTTC A CTGCCGAGA AAACCGTGT  
 3451 TTGGATTCTT TGACCCGGGA ACTTAATGTC GTTCTCAGC AGCTGTGTGA  
 AACCTAAGAA ACTGGGCCCT TGAATTACAG CAAAGAGTCG TCGACAACCT  
 3501 TCTGCGCCAG CAGGTTTCTG CCCTGAAGGC TTCTCCCTT CCCAATGCGG  
 AGACGCGGTC GTCCAAGAC GGGACTTCG AAGGAGGGGA GGGTTACGCC  
 3551 TTTAAACAT AAATAAAAA CCAGACTCTG TTTGGATTG GATCAAGCA  
 AAATTTTGT TTTATTTTT GGTCTGAGAC AAACCTAAAC CTAGTTCGT  
 3601 GTGCTTTGCT GTCITTTATT AGGGGTTTTG CGCGCGCGGT AGGCCCGGA  
 CACAGAACGA CAGAAATAA TCCCCAAAC GCGCGCGCCA TCCGGGCCCT  
 3651 CCAGCGGTCT CGGTCTGTGA GGTCTCTGTG TATTTTTTCC AGGACGTGT  
 GGTGCGCAGA GCCAGCACT CCCAGGACAC ATAAAAAGG TCTGCACCA  
 3701 AAAGGTGACT CTGGATGTTG AGATACATGG GCATAAGCCC GTCTCTGGG  
 TTCCACTGA GACCTACAAG TCTATGTACC CGTATTCGGG CAGAGACCCC  
 3751 TGGAGGTAGC ACCACTGCAG AGCTTCATGC TGGGGGGTGG TGTGTAGAT  
 ACCTCCATCG TGGTGACGTC TCGAAGTACG ACGCCCCACC ACAACATCTA  
 3801 GTACCAAGTC TAGCAGGAGC GCTGGGCGTG GTGCCTAAAA ATGCTTTCA  
 CTAGGTGAGC ATGCTCTCG CGACCCGCAC CACGGATTTT TACAGAAAGT  
 3851 GTAGCAAGCT GATTGCCAGG GGCAGGCCCT TGGTGAAGT GTTTACAAAG  
 CATCGTTTGA CTAACGCTCC CCGTCCGGGA ACCACATTCA CAAATGTTTC  
 3901 CGGTTAAGCT GGGATGGGTG CATACGTGGG GATATGAGAT GCATCTTGA  
 GCCAATTCGA CCTACCCAC GTATGCACCC CTATACTCTA CGTAGAACCT  
 3951 CTGTATTTTT AGSTTGGCTA TGTTCCAGC CATATCCCTC CGGGGATTCA  
 GACATAAAAA TCCAACCGAT ACAAGGGTGC GTATAGGGAG GCCCTAAGT  
 4001 TGTGTGTCAG AACCACCAGC ACAGTGTATC CGGTGCACCT GGGAAATTG  
 ACAACACGTC TTGGTGGTCG TGTCACATAG GCCACGTGA CCCCTTAAC  
 4051 TCATGTAGCT TAGAAGGAAA TGCGTGGGAG AACTTGGAGA CGCCCTTGTG  
 AGTACATCGA ATCTTCCTTT ACGCACCTTC TTGAACCTCT GCGGGAACAC  
 4101 ACCTCCAAGA TTTTCCATGC ATTCTGTCAT AATGATGGCA ATGGGCCAC  
 TGGAGTTCT AAAAGGTACG TAAGCAGGTA TTACTACCGT TACCCGGGTG  
 4151 GGGCGGGCGC CTGGGCGAAG ATATTCTTGG GATCACTAAC GTCATAGTTG  
 CCCGCCGCCG GACCCGCTTC TATAAGACC CTAGTGATTG CAGTATCAAC

FIG.9A-5

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4201 TGTCCAGGA TGAGTCGTC ATAGGCCATT TTTACAAAGC GCGGGCGGAG  
 ACAAGGTCCT ACTCTAGCAG TATCCGGTAA AAATGTTTCG CGCCCGCCTC  
 4251 GGTGCCAGAC TGCGGTATAA TGGTTCCATC CGGCCAGGG GCGTAGTTAC  
 CCACGGCTG ACGCCATATT ACCAAGTAG GCCGGGTCCC CGCATCAATG  
 4301 CCTACAGAT TTGCATTTCC CACGCTTTGA GTTCAGATGG GGGGATCATG  
 GGAGTGCTA AACGTAAAGG GTGCAAACT CAAGTCTACC CCCCTAGTAC  
 4351 TCTACCTGCG GGGCGATGAA GAAAACGGTT TCCGGGGTAG GGGAGATCAG  
 AGATGGACGC CCCGCTACTT CTTTGGCAA AGGCCCATC CCCTCTAGTC  
 4401 CTGGGAAGAA AGCAGGTTCC TGAGCAGCTG CGACTTACC GAGCCGGTGG  
 GACCCTTCTT TCGTCCAAGG ACTGTCGAC GCTGAATGGC GTCGGCCACC  
 4451 GCCCGTAAAT CACACCTATT ACCGGCTGCA ACTGGTAGTT AAGAGAGCTG  
 CGGGCATTTA GTGTGGATAA TGGCCGACGT TGACCATCAA TTCTCTCGAC  
 4501 CAGCTGCCGT CATCCCTGAG CAGGGGGGCC ACTTCGTAA GCATGTCCCT  
 GTCGACGGCA GTAGGGACTC GTCCCCCGG TGAAGCAATT CGTACAGGGA  
 4551 GACTCGCATG TTTTCCCTGA CCAAATCCGC CAGAAGGCGC TCGCCGCCCA  
 CTGAGCGTAC AAAAGGACT GGTTTAGCG GTCTCCGCG AGCGCGGGT  
 4601 GCGATAGCAG TTCTTGCAAG GAAGCAAAGT TTTTCAACGG TTTGAGACCG  
 CGCTATCGTC AAGAACGTTT CTTCTTTTCA AAAAGTTGCC AAACCTTGGC  
 4651 TCCGCGGTAG GCATGCTTTT GAGCGTTTGA CCAAGCAGTT CCAGGCGGTC  
 AGGGCGCATC CGTACGAAAA CTCGCAAACT GGTTCGTCAA GGTCCGCCAG  
 4701 CCACAGCTCG GTCACCTGCT CTACGGCATC TCGATCCAGC ATATCTCCTC  
 GGTGTCGAGC CAGTGGACGA GATGCCGTAG AGCTAGGTG TATAGAGGAG  
 4751 GTTTCCGCGG TTGGGGCGGC TTTGCTGTA CGGCAGTAG CGGTGCTCGT  
 CAAAGCGCCC AACCCGCGG AAAGCGACAT GCCGTCATCA GCCACGAGCA  
 4801 CCAGACGGG CAGGGTCATG TCTTTCCAGC GGGCAGGGT CCTGTCAGC  
 GGTCTGCCCG GTCCAGTAC AGAAAGGTGC CCGGCTCCA GAGCAGTCTG  
 4851 GTAGTCTGGG TCACGGTGAA GGGGTGCGCT CCGGCTGCG CGGTGCGGAG  
 CATCAGACC AGTGCCACTT CCCACGCGA GGCCGACGC GCGACCGGTC  
 4901 GGTGCGCTTG AGGCTGGTCC TGCTGGTGCT GAAGCGTGC CGGTCTTCGC  
 CCACGCGAAC TCCGACCAGG ACGACCACGA CTTGCGAGC GCCAGAGCG  
 4951 CCTGCGGCTC GGCCAGGTAG CATTTGACCA TGGTGTCATA GTCCAGCCCC  
 GGACGCGAG CCGGTCCATC GTAAACTGAT ACCACAGTAT CAGGTGCGGG  
 5001 TCCGCGGCGT GGCCCTTGGC GCGCAGCTTG CCTTGGAGG AGGCGCGCGA  
 AGGCGCCGCA CCGGGAACCG CGCGTCGAAC GGAACCTTC TCCGCGGCGT

FIG.9A-6

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5051 CGAGGGGCGAG TGCAGACTTT TGAGGGCGTA GAGCTTGGGC GCGAGAAATA  
 GCTCCCCGTC ACGTCTGAAA ACTCCCGCAT CTCGAACCCG CGCTCTTTAT  
 5101 CCGATTCCGG GGAGTAGGCA TCCGCGCCGC AGGCCCGCA GACGGTCTCG  
 GGCTAAGGCC CCTCATCCGT AGGCGCGGCG TCCGGGCGT CTGCCAGAGC  
 5151 CATTCCACGA GCCAGGTGAG CTCTGGCCGT TCGGGGTCAA AAACAGGTT  
 GTAAGGTGCT CGGTCCACTG GAGACCGCA AGCCCCAGTT TTTGGTCCAA  
 5201 TCCCCCATGC TTTTGTATGC GTTCTTACC TCTGGTTTCC ATGAGCCGGT  
 AGGGGGTACG AAAAATACG CAAAGAATGG AGACCAAAGG TACTCGGCCA  
 5251 GTCCACGCTC GGTGACGAAA AGGCTGTCCG TGTCCCCGTA TACAGACTTG  
 CAGGTGCGAG CCACTGCTTT TCCGACAGGC ACAGGGGCAT ATGTCTGAAC  
 5301 AGAGGCTGT CCTCGAGCGG TGTTCGCGG TCCTCCTCGT ATAGAACTC  
 TCTCCGACA GGAGCTCGCC ACAAGGCGCC AGGAGGAGCA TATCTTTGAG  
 5351 GGACCACTCT GAGACAAAGS CTCGCTCCA GGCCAGCAGC AAGGAGGCTA  
 CCTGGTGAGA CTCTGTTTCC GAGCGCAGGT CCGTGTGTGC TTCCTCCGAT  
 5401 AGTGGGAGGG GTAGCGGTCTG TTGTCCACTA GGGGGTCCAC TCGTCCAGG  
 TCACCTCCC CATCGCCAGC AACAGTGAT CCCCAGGTG AGCGAGGTCC  
 5451 GTGTGAAGAC ACATGTCGCC CTCTTCGGCA TCAAGGAAGG TGATTGGTTT  
 CACACTTCTG TGTACAGCGG GAGAAGCCGT AGTTCTTCC ACTAACCAAA  
 5501 GTAGGTGTAG GCCACGTGAC CGGGTGTTC TGAAGGGGGG CTATAAAAGG  
 CATCCACATC CGGTGCACTG GCCACAAGG ACTTCCCCC GATATTTTCC  
 5551 GGGTGGGGGC GCGTTCGTCC TCACTCTCTT CCGCATCGCT GTCTGCGAGG  
 CCCACCCCG CGCAAGCAGG AGTGAGAGAA GCGGTAGCGA CAGACGCTCC  
 5601 GCCAGCTGTT GGGGTGAGTA CTCCTCTGA AAAGCGGGCA TGACTTCTGC  
 CGGTGCAAA CCCCACTCAT GAGGGAGACT TTTCGCCGT ACTGAAGACG  
 5651 GCTAAGATTG TCAGTTTCCA AAAACGAGGA GGATTTGATA TTCACCTGGC  
 GATTCTAAC AGTCAAAGGT TTTTGCTCCT CCTAACTAT AAGTGGACCG  
 5701 CCGCGGTGAT GCCTTTGAGG GTGGCCGCAT CCATCTGGTC AGAAAAGACA  
 GGCGCCACTA CGGAACTCC CACCGCGTA GGTAGACCAG TCTTTTCTGT  
 5751 ATCTTTTTGT TGTCAAGCTT GGTGGCAAA GACCCGTAGA GGGGTTGGA  
 TAGAAAAACA ACAGTTTCGA CCACCGTTTG CTGGGCATCT CCCGCAACCT  
 5801 CAGCAACTTG GCGATGGAGC GCAGGGTTTG GTTTTTGTGC CGATCGGCGC  
 GTCGTTGAAC CGCTACCTCG CGTCCAAAC CAAAAACAGC GCTAGCCGCG  
 5851 GCTCCTTGGC CGCGATGTTT AGCTGCAGT ATTGCGCGC AACGCACCGC  
 CGAGGAACCG CGCTACAAA TCGAGTGCA TAAGCGCGC TTGCGTGGCG

FIG.9A-7

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5901 CATTGGGAA AGACGGTGGT GCGCTCGTCG GGCACCAAGT GCACGCGCCA  
 GTAAGCCCTT TCTGCCACCA CGCGAGCAGC CCGTGGTCCA CGTGGCGGGT  
 5951 ACCGCGGTG TGCAGGGTGA CAAGGTCAAC GCTGGTGGCT ACCTCTCCGC  
 TGGCGCCAAC ACGTCCCACT GTTCCAGTTG CGACCACCGA TGGAGAGGCG  
 6001 GTAGGCGCTC GTTGGTCCAG CAGAGGCGGC CGCCCTTGCG CGAGCAGAAT  
 CATCCGCGAG CAACCAGGTC GTCTCGCCG CGGGGAACGC GCTCGTCTTA  
 6051 GCGGGTAGGG GGTCTAGCTG CGTCTCGTCC GGGGGGTCTG CGTCCACGGT  
 CGCCATCCC CCAGATCGAC GCAGAGCAGG CCCCCAGAC GCAGGTGCCA  
 6101 AAAGACCCCG GGCAGCAGGC GCGCGTCGAA GTAGTCTATC TTGCATCCTT  
 TTTCTGGGGC CCGTCGTCCG CGCGCAGCTT CATCAGATAG AACGTAGGAA  
 6151 GCAAGTCTAG CGCCTGCTGC CATGCGCGGG CGGCAAGCGC GCGCTCGTAT  
 CGTTCAGATC GCGGACGACG GTACGCGCCC GCGTTCGCG CGCGAGCATA  
 6201 GGGTTGAGTG GGGGACCCCA TGGCATGGGG TGGGTGAGCG CGGAGGCGTA  
 CCCAACTCAC CCCCTGGGGT ACCGTACCCC ACCCACTCGC GCCTCCGCAT  
 6251 CATGCCGCAA ATGTCGTAAA CGTAGAGGGG CTCTCTGAGT ATTCCAAGAT  
 GTACGGCGTT TACAGCATTT GCATCTCCCC GAGAGACTCA TAAGGTTCTA  
 6301 ATGTAGGGTA GCATCTTTCCA CCGCGGATGC TGGCGCGCAC GTAATCGTAT  
 TACATCCCAT CGTAGAAGGT GGCGCCACG ACCGCGCGTG CATTAGCATA  
 6351 AGTTCGTGCG AGGGAGCGAG GAGGTGCGGA CCGAGGTTGC TACGGGCGGG  
 TCAAGCACGC TCCTCGCTC CTCAGCCCT GGCCTCAACG ATGCCCGCCC  
 6401 CTGCTCTGCT CGGAAGACTA TCTGCCTGAA GATGCGATGT GAGTTGGATG  
 GACGAGACGA GCCTTCTGAT AGACGGACTT CTACCGTACA CTC AACCTAC  
 6451 ATATGGTTGG ACGCTGGAAG ACGTTGAAGC TGGCGTCTGT GAGACCTACC  
 TATACCAACC TCGACCTTC TGCAACTTCG ACCGCGAGACA CTCTGGATGG  
 6501 GCGTCACGCA CGAAGGAGGC GTAGGAGTCG CGCAGCTTGT TGACCACTC  
 GCGAGTGCST GCTTCTCCG CATCTCAGC GCGTCGAAAC ACTGTCGAG  
 6551 GCGGTGACC TGCACGTCTA GGGCGCAGTA GTCCAGGGTT TCCTTGATGA  
 CCGCCACTGG ACGTGCAGAT CCGCGTCAT CAGGTCCCAA AGGAACCTACT  
 6601 TGTCACTATT ATCCTGTCCC TTTTTTTTCC ACAGCTCGCG GTTGAGGACA  
 ACGATATGAA TAGGACAGGG AAAAAAAGG GTTCGAGCGC CAACTCCTGT  
 6651 AACTCTTCGC GGTCTTTTCCA GTACTCTTGG ATCGGAAACC CGTCGGCCTC  
 TTGAAGAAGC CCAGAAAGGT CATGAGAACC TAGCCTTTGG GCAGCCGGAG  
 6701 CGAACGGTAA GAGCCTAGCA TGTAAGACTG GTTGACGGCC TGGTAGGCGC  
 GCTTGCCATT CTCGGATCGT ACATCTTGAC CAACTGCCGG ACCATCCGCG

FIG. 9A-8

17/70

6751 AGCATCCCTT TTCTACGGGT AGCGCGTATG CCTGCGCGGC CTTCCGGAGC  
 TCGTAGGGAA AAGATGCCCA TCGCGCATAC GGACGCGCCG GAAGGCCTCG  
 6801 GAGGTGTGGG TGAGCGCAAA GGTGTCCCTG ACCATGACTT TGAGGTACTG  
 CTCACACCC ACTCGCGTTT CCACAGGGAC TGGTACTGAA ACTCCATGAC  
 6851 GTATTTGAAG TCAGTGTGCT CGCATCCGCC CTGCTCCAG AGCAAAAGT  
 CATAAACTC AGTCACAGCA GCGTAGGCGG GACGAGGGTC TCGTTTTTCA  
 6901 CCGTGCGCTT TTTGGAACGC GGATTGGCA GGGCGAAGGT GACATCGTTG  
 GGCACGCGAA AAACCTTGCG CTTAAACCGT CCCGCTTCCA CTGTAGCAAC  
 6951 AAGAGTATCT TTCCCGCGCG AGGCATAAAG TTGCGTGTGA TGGGAAGGG  
 TTCTCATAGA AAGGGCGCGC TCCGTATTTT AACGCACACT ACGCCTTCCC  
 7001 TCCCGGCACC TCGGAACGGT TGTTAATTAC CTGGGCGGCG AGCAGCATCT  
 AGGGCCGTGG AGCCTTGCCA ACAATTAATG GACCCGCGCG TCGTGTAGTA  
 7051 CGTCAAAGCC GTTGATGTTG TGGCCACAA TGTAAGTTC CAAGAAGCGC  
 GCAGTTTCGG CAACTACAAC ACCGGGTGTT ACATTTCAAG GTTCTTCGCG  
 7101 GGGATGCCCT TGATGGAAGG CAATTTTTTA AGTTCTCTGT AGGTGAGCTC  
 CCCTACGGGA ACTACCTTCC GTTAAAAAT TCAAGAGCA TCCACTCGAG  
 7151 TTCAGGGGAG CTGAGCCCGT GCTCTGAAAG GGCCAGTCT GCAAGATGAG  
 AAGTCCCCTC GACTCGGGCA CGAGACTTTC CCGGTGAGA CGTTCTACTC  
 7201 GGTGGAAGC GACGAATGAG CTCCACAGGT CACGGCCAT TAGCATTGCG  
 CCAACCTTCG CTGCTTACTC GAGGTGTCCA GTGCCCGGTA ATCGTAAACG  
 7251 AGGTGGTCGC GAAAGGTCTT AAATGGCGA CCTATGGCCA TTTTCTCTGG  
 TCCACCAGCG CTTTCCAGGA TTTGACCGCT GGATACCGGT AAAAAAGACC  
 7301 GGTGATGCAG TAGAAGGTAA GCGGTCTTGG TTCCAGCGCG TCCATCCAA  
 CCACTACGTC ATCTTCCATT CGCCAGAAC AAGGTGCGCC AGGGTAGGTT  
 7351 GGTTCGCGCG TAGGTCTCGC GCGGCAGTCA CTAGAGGCTC ATCTCCGCGG  
 CCAAGCGCGG ATCCAGAGCG CGCGTCAGT GATCTCCGAG TAGAGGCGCG  
 7401 AACTTCATGA CCAGCATGAA GGCACGAGC TGCTTCCCAA AGGCCCCAT  
 TTGAAGTACT GGTGTAAGT CCGGTGCTCG ACGAAGGTT TCCGGGGTGA  
 7451 CCAAGTATAG GTCTCTACAT CGTAGGTGAC AAAGAGACGC TCGGTGCGAG  
 GGTTCATATC CAGAGATGTA GCATCCACTG TTTCTCTGCG AGCCACGCTC  
 7501 GATGCGAGCC GATCGGGAAG AACTGGATCT CCCGCCACCA ATTGGAAGGAG  
 CTACGCTCGG CTAGCCCTTC TTGACCTAGA GGGCGGTGGT TAACCTCTCT  
 7551 TGGCTATTGA TGTGGTGAAG GTAGAAGTCC CTGCGACGGG CCGAACACTC  
 ACCGATAACT ACACCACTTT CATCTTCAGG GACGCTGCCC GGCTGTGAG

FIG.9A-9

18/70

7601 GTGCTGGCTT TTGTAAAAAC GTGCGCAGTA CTGGCAGCGG TGCACGGGT  
 CACGACCGAA AACATTITTTG CACGCGTCAT GACCGTCGCC ACGTGCCCGA  
 7651 GTACATCCTG CACGAGGTTG ACCTGACGAC CGCGCACAAAG GAAGCAGAGT  
 CATGTAGGAC GTGCTCCAAC TGGACTGCTG GCGCGTGTTT CTTCGCTCTA  
 7701 GGGAAATTGA GCCCCTCGCC TGGCGGGTTT GCGTGGTGGT CTTTACTTTC  
 CCTTTAACT CGGGGAGCGG ACCGCCCAA CCGACCACCA GAAGATGAAG  
 7751 GCGTGTCTGT CCTTGACCGT CTGGCTGCTC GAGGGGAGTT ACGGTGGATC  
 CCGACGAACA GGAAC TGGA GACCGACGAG CTCCCTCAA TGCCACCTAG  
 7801 GGACCACCAC GCGCGCGGAG CCCAAAGTCC AGATGTCCGC GCGCGCGCGT  
 CCTGGTGGTG GCGCGCGCTC GGGTTTCAGG TCTACAGGCG CGCGCCCGCA  
 7851 CGGAGCTTGA TGACAACATC GCGCAGATGG GAGCTGTCCA TGGTCTGGAG  
 GCCTCGAACT ACTGTTGTAG CGGTCTACC CTCGACAGGT ACCAGACCTC  
 7901 CTCCCGCGGC GTCAGGTCAG GCGGGAGCTC CTCGAGTTT ACCTCGCATA  
 GAGGGCGCGC CAGTCCAGTC CGCCCTCGAG GACGTCCAAA TGGAGCGTAT  
 7951 GACGGGTCTAG GCGCGCGGCT AGATCCAGGT GATACCTAAT TTCCAGGGGC  
 CTGCCAGTC CGCGCCCGA TCTAGGTCCA CTATGATTA AAGTCCCGCG  
 8001 TGTTTGGTGG CGGCGTCGAT GGCTTGCAAG AGGCGCATC CCCGCGCGC  
 ACCAACCCACC GCCGCGACTA CCGAACGTTC TCCGGCGTAG GGGCGCGCG  
 8051 GACTACGGTA CCGCGCGGCG GCGGGTGGG CGCGGGGGTG TCCTTGGATG  
 CTGATGCCAT GCGCGCGCGC CGGCCACCG CGCGCCCGAC AGGAACCTAC  
 8101 ATGCATCTAA AAGCGGTGAC GCGGGCGAGC CCCCGAGGT AGGGGGGGCT  
 TACGTAGATT TTCGCCACTG CGCCCGCTCG GGGGCCCTCA TCCCCCGCA  
 8151 CCGGACCCGC CGGAGAGGG GCGAGGGCA CGTCGCGGCC GCGCGCGGGC  
 GGCCTGGGCG GCCCTCTCCC CCGTCCCCTG GCAGCCGCGG CGCGCGCCCG  
 8201 AGGAGCTGGT GCTGCGCGCG TAGGTTGCTG GCGAACGCGA CGACGCGGCG  
 TCCTCGACCA CGACGCGCGC ATCCAACGAC CGCTTGCGCT GCTGCGCCCG  
 8251 GTTGATCTCC TGAATCTGGC GCGTCTGCGT GAAGACGACG GCGCCGGTGA  
 CAACTAGAGG ACTTAGACCG CGGAGACGCA CTCTGCTGCG CCGGCCACT  
 8301 GCTTGAACCT GAAAGAGAGT TCGACAGAAT CAATTTCCGT GTCGTTGACG  
 CGAATCTTGA CTTTCTCTCA AGCTGTCTTA GTTAAAGCCA CAGCAACTGC  
 8351 GCGGCCCTGGC GCAAAATCTC CTGACGTCT CCTGAGTTGT CTTGATAGCG  
 CGCCGACCG CGTTTTAGAG GACGTGCAGA GGAATCAACA GAATATCCG  
 8401 GATCTCGGCC ATGAAGTCTC CGATCTCTTC CTCTGGAGA TCTCCGCGTC  
 CTAGAGCCGG TACTTGACGA GCTAGAGAAG GAGGACCTCT AGAGGCGCAG

FIG.9A-10

19/70

8451 CGGCTCGCTC CACGGTGGCG GCGAGGTCGT TGGAAATGCG GGCCATGAGC  
 GCCGAGCGAG GTGCCACCGC CGCTCCAGCA ACCTTTACGC CCGGTACTCG  
 8501 TGCAGAAAGG CGTTGAGGCC TCCCTCGTTC CAGACGCGGC TGTAGACCAC  
 ACGCTCTTCC GCAACTCCGG AGGGAGCAAG GTCTGCGCCG ACATCTGGTG  
 8551 GCCCCCTTCG GCATCGCGGG CGCGCATGAC CACCTGCGCG AGATTGAGCT  
 CGGGGGAAGC CGTAGCGCCC GCGGTACTG GTGACGCGC TCTAACTCGA  
 8601 CCAGTGC CGGCAAGACG GCGTAGTTTC CGAGCGCGTG AAAGAGGTAG  
 GGTGACGGC CGCTTCTGCG CGCATCAAAG CGTCCGCGAC TTCTTCCATC  
 8651 TTGAGGGTGG TGGCGGTGTG TTCTGCCACG AAGAAGTACA TAACCCAGCG  
 AACTCCACCC ACCGCCACAC AAGACGGTGC TTCTTCATGT ATTGGGTCGC  
 8701 TCGCAACGTG GATTGTTGA TATCCCCAA GGCCTCAAGG CGCTCCATGG  
 AGCGTTGCAC CTAAGCAACT ATAGGGGGTT CCGGAGTTCC GCAGGGTACC  
 8751 CCTCGTAGAA GTCCACGGCG AAGTTGAAAA ACTGGGAGTT GCGCGCCGAC  
 GGAGCATCTT CAGGTGCCGC TTCAACTTTT TGACCCTCAA CGCGCGGCTG  
 8801 ACGGTTAACT CCTCCTCCAG AAGACGGATG AGCTCGCGCA CAGTGTGCGG  
 TGCCAATTGA GGAGGAGTGC TTCTGCCTAC TCGAGCGCCT GTCACAGCGC  
 8851 CACCTCGCGC TCAAAGGCTA CAGGGGCTC TTCTTTCTCT TCAATCTCCT  
 GTGGAGCGCG AGTTTCCGAT GTCCCCGGAG AAGAAGAAGA AGTTAGAGGA  
 8901 CTTCATAAG GGCTCCCTCT TCTTCTTCTT CTGGCGCGGG TGGGGAGGGG  
 GAAGGTATTC CCGGAGGGGA AGAAGAAGAA GACCGCGCGC ACCCCCTCCC  
 8951 GGGACACGGC GGCACGACG GCGCACC6GG AGGCGGTCTG CAAAGCGCTC  
 CCTGTGCCG CCGCTGCTGC GCGGTGGCCC TCCGCCAGCT GTTTCGCGAG  
 9001 GATCATCTCC CCGCGGCGAC GGCATGATGT CTCGTTGACG GCGCGGCCGT  
 CTAGTAGAGG GCGCGCCGCTG CCGGTACCA GAGCCACTGC CCGCGCCGCA  
 9051 TCTCGCGGGG GCGCAGTTGG AAGACGCCG CCGTCATGTC CCGGTTATGG  
 AGAGCGCCCC CCGTCAACC TTCTCGGGCG GCGAGTACAG GGCAATACCT  
 9101 GTTGGCGGGG GGCTGCCATG CCGCAGGGAT ACGGCGCTAA CGATGCATCT  
 CAACCGCCCC CCGACGTGAC GCGGTCCCTA TGCCGCGATT GCTACGTAGA  
 9151 CAACAATTGT TGTGTAGGTA CTCGCCGCCG GAGGGACCTG AGCGAGTCCG  
 GTTGTAAACA ACACATCCAT GAGGCGGCGG CTCCTGGAC TCGCTCAGGC  
 9201 CATCGACCGG ATCGGAAAAC CTCTCGAGAA AGCGTCTAA CCAGTCACAG  
 GTAGCTGGCC TAGCTTTTGG GAGAGCTCTT TCCGAGATT GGTGAGTGTG  
 9251 TCGCAAGGTA GGCTGAGCAC CGTGGCGGGC GGCAGCGGGC GCGGTGCGG  
 AGCGTTCCAT CCGACTCGTG GCACCGCCCG CCGTGGCGCG CCGCCAGCCC

FIG.9A-11

20/70

9301 GTTGTTCCTG GCGGAGGTGC TGCTGATGAT GTAATTAAAG TAGCGGTCT  
 CAACAAAGAC CGCCTCCACG ACGACTACTA CATTAAATTC ATCCGCCAGA  
 9351 TGAGACGGCG GATGGTCGAC AGAAGCACCA TGTCTTGGG TCCGGCTGC  
 ACTCTGCCGC CTACCAAGCTG TCTTCGTGGT ACAGGAACCC AGGCCGAGCG  
 9401 TGAATGCCGA GCGGTCGCG CATGCCCCAG GCTTCGTTTT GACATCGGCG  
 ACTTACCGGT CCGCCAGCCG GTACGGGGTC CGAAGCAAAA CTGTAGCCCG  
 9451 CAGGTCCTTG TAGTAGTCTT GCATGAGCCT TTCTACCGGC ACTTCTTCTT  
 GTCCAGAAAC ATCATCAGAA CGTACTCGGA AAGATGGCCG TGAAGAAGAA  
 9501 CTCCTTCCTC TTGTCTTGCA TCTCTTGCA CTATCGTGC GCGCGCGCG  
 GAGGAAGGAG AACAGGACGT AGAGAACGTA GATAGCGACG CCGCCGCGCG  
 9551 GAGTTTGCC GTAGGTGGCG CCCTCTTCCT CCCATGCGTG TGACCCCGAA  
 CTCAAACCG CATCCACCGC GGGAGAAGGA GGGTACGCAC ACTGGGCTT  
 9601 GCCCTCATC GGCTGAAGCA GGGCTAGGTC GGCACAACG CGCTCGGCTA  
 CGGGGAGTAG CCGACTTCGT CCCGATCCAG CCGCTGTTGC GCGAGCCGAT  
 9651 ATATGGCCTG CTGCACCTGC GTGAGGGTAG ACTGGAAGTC ATCCATGTCC  
 TATACCGGAC GACGTGGACG CACTCCCATC TGACCTTCAG TAGGTACAGG  
 9701 ACAAGCGGT GGTATGCGCC CGTGTGATG GTGTAAGTGC AGTTGGCCAT  
 TGTTCGCCA CCATACGCGG GCACAACTAC CACATTCACG TCAACCGSTA  
 9751 AACGGACCAG TTAACGGTCT GGTGACCCGG CTGCGAGAGC TCGGTGTACC  
 TTGCCTGGTC AATTGCCAGA CCACTGGGCC GACGCTCTCG AGCCACATGG  
 9801 TGAGACGCGA GTAAGCCCTC GAGTCAAATA CGTAGTCGTT GCAAGTCCGC  
 ACTCTCGCT CATTGCGGAG CTCAGTTTAT GCATCAGCAA CGTTCAGGCG  
 9851 ACCAGGTA CTGATCCAC CAAAAGTGC GCGCGCGGCT GCGGTTAGAG  
 TGGTCCATGA CCATAGGGTG GTTTTTCACG CCGCGCCGA CCGCATCTC  
 9901 GGGCCAGCGT AGGGTGGCCG GGGCTCCGGG GCGGAGATCT TCCAACATAA  
 CCGGCTCGCA TCCACCGGCG CCGAGGCC CCGCTCTAGA AGGTTGTATT  
 9951 GCGCATGATA TCCGTAGATG TACCTGGACA TCCAGGTGAT GCCGCGCGCG  
 CCGCTACTAT AGGCATCTAC ATGGACCTGT AGGTCCACTA CCGCGCGCGC  
 10001 GTGGTGGAGG CGCGCGGAAA GTCGCGGACG CGGTTCCAGA TGTTCGCGAG  
 CACCACCTCC GCGCGCTTT CAGCGCTGC GCCAAGGTCT ACACGCGTC  
 10051 CGGCAAAAAG TGCTCCATGG TCGGACGCT CTGCGCGGTC AGGCGCGCGC  
 GCCGTTTTT ACAGGATACC AGCCCTGCGA GACCGGCCAG TCCGCGCGCG  
 10101 AATCGTTGAC GCTCTAGACC GTGCAAAAGG AGAGCTGTA AGCGGGCACT  
 TTAGCAACTG CGAGATCTGG CACGTTTTCC TCTCGGACAT TCGCCCGTGA

FIG.9A-12

21/70

10151 CTTCCGTGGT CTGGTGGATA AATTCGCAAG GGTATCATGG CGGACGACCG  
 GAAGGACCA GACCACCTAT TTAAGCGTTC CCATAGTACC GCCTGCTGGC  
 10201 GGGTTCCGAGC CCCGTATCCG GCCGTCCGCC GTGATCCATG CGGTATCCGC  
 CCCAAGCTCG GGGCATAGGC CGGCAGGCGG CACTAGGTAC GCCAATGGCG  
 10251 CCGCGTGTCTG AACCCAGGTG TGCAGCTCA GACAACGGGG GAGTGTCTCT  
 GGCACACAGC TTGGGTCCAC ACGCTGCAGT CTGTTGCCCC CTCACGAGGA  
 10301 TTTGGCTTCC TTCCAGGCGC GCGGCGTGCT GCGCTAGCTT TTTTGCCAC  
 AAACCGAAGG AAGGTCCGCG CGCGGACGA CGCGATCGAA AAAACCGGTG  
 10351 TGGCCGCGCG CAGCGTAAGC GGTTAGGCTG GAAAGCGAAA GCATTAAGTG  
 ACCGGCGCGC GTCGATTCC CCAATCCGAC CTTTCGCTTT CGTAATTCAC  
 10401 GCTCGCTCCC TGTAGCCGGA GGGTTATTTT CCAAGGGTTG AGTCGCGGGA  
 CGAGCGAGGG ACATCGGCTT CCAATAAAA GGTTCACAA TCAGCGCCCT  
 10451 CCCCCGGTTC GAGTCTCGGA CCGGCGGAC TCGGCGGAAC GGGGGTTTGC  
 GGGGGCCAAG CTCAGAGCCT GCGCGGCTG ACGCCGCTTG CCCCCAACG  
 10501 CTCGCCGTCA TGCAGACCC CGCTTGCAAA TTCTCCGGA AACAGGGACG  
 GAGGGGAGT ACGTTCGCG GCGAACGTTT AAGGAGGCT TTGTCCTCGC  
 10551 AGCCCCTTTT TTGCTTTTCC CAGATGCATC CGGTGCTGCG GCAGATGCGC  
 TCGGGGAAAA AACGAAAAGG GTCTACGTAG GCCACGACGC CGTCTACGCG  
 10601 CCCCTCCTC AGCAGCGGCA AGAGCAAGAG CAGCGGAGA CATGACGGG  
 GGGGGAGGAG TCGTCGCCGT TCTCGTTCTC GTCGCCGTCT GTACGTCCCG  
 10651 ACCCTCCCCT CCTCTACCG CGTCAGGAGG GCGGACATCC GCGGTTGACG  
 TGGGAGGGGA GGAGGATGGC GCAGTCTCC CCGCTGTAGG CGCCAACTGC  
 10701 CCGCAGCAGA TGGTGATTAC GAACCCCGC GCGCCCGGG CCGGCACTAC  
 GCCGTGCTCT ACCACTAATG CTTGGGGGCG CCGCGGCCG GCGCGTGATG  
 10751 CTGGACTTGG AGGAGGGCGA GGGCTGGCG CGGCTAGGAG CGCCCTCTCC  
 ACGCTGAACC TCCTCCGCTT CCGGACCGC GCCGATCTC GCGGAGAGGG  
 10801 TGAGCGGCAC CCAAGGGTGC AGCTGAAGCG TGATACGCGT GAGGCGTACG  
 ACTCGCCGTG GGTTCACAG TCGACTTCGC ACTATGCGCA CTCGCGATGC  
 10851 TGCAGCGGCA GAACCTGTTT CGCGACCGCG AGGAGAGGA GCCCGAGGAG  
 ACGCGCGCGT CTTGGACAAA CGCGTGGCG TCCTCTCCT CGGGCTCCTC  
 10901 ATGCGGGATC GAAAGTTCCA CGCAGGGCGC GAGCTGCGGC ATGCGCTGAA  
 TACGCCCTAG CTTTCAAGGT GCGTCCGCG CTGACGCGG TACCGGACTT  
 10951 TCGCGAGCGG TTGCTGCGCG AGGAGGACTT TGAGCCCGAC GCGCGAACCG  
 ACGGCTCGCC AACGACGCGC TGCTCTGAA ACTCGGGCTG CGCGCTTGGC

FIG.9A-13

22/70

11001	GGATTAGTCC CCTAATCAGG	CGCGCGCGCA GCGCGCGCGT	CACGTGGCGG GTGCACCGCC	CCGCCGACCT GCGCGCTGGA	GGTAACCGCA CCATTGGCGT
11051	TACGAGCAGA ATGCTCGTCT	CGGTGAACCA GCCACTTGGT	GGAGATTAAC CCTCTAATTG	TTTCAAAAAA AAAGTTTTTT	GCTTTAACAA CGAAATTTGT
11101	CCACGTGCGT GGTGACGCA	ACGCTTGTGG TGCGAACACC	CGCGCGAGGA GCGCGCTCCT	GGTGGCTATA CCACCGATAT	GGACTGATGC CCTGACTACG
11151	ATCTGTGGGA TAGACACCCT	CTTTGTAAGC GAAACATTCG	GCGCTGGAGC GCGGACCTCG	AAAACCCAAA TTTTGGGTTT	TAGCAAGCCG ATCGTTCGGC
11201	CTCATGGCGC GAGTACCGCG	AGCTGTTCCCT TCGACAAGGA	TATAGTGCAG ATATCACGTC	CACAGCAGGG GTGTCTGCC	ACAACGAGGC TGTGTCTCCG
11251	ATTCAGGGAT TAAGTCCCTA	GCGCTGCTAA CGCGACGATT	ACATAGTAGA TGTATCATCT	GCCCCAGGGC CGGGCTCCCG	CGCTGGCTGC GCGACCGACG
11301	TCGATTTGAT AGCTAAACTA	AAACATCCTG TTTGTAGGAC	CAGAGCATAG GTCTCGTATC	TGGTGCAGGA ACCACGTCTT	GCGCAGCTTG CGCGTCGAAC
11351	AGCCTGGCTG TCGGACCGAC	ACAAGGTGGC TGTCCACCG	CGCCATCAAC GCGGTAGTTG	TATTCCATGC ATAAGGTACG	TTAGCCTGGG AATCGGACCC
11401	CAAGTTTATC GTTCAAAATG	GCCCGCAAGA CGGGCGTTCT	TATACCATAC ATATGGTATG	CCCTTACGTT GGGAATGCAA	CCCATAGACA GGGTATCTGT
11451	AGGAGGTAAA TCTCCATTT	GATCGAGGGG CTAGCTCCCC	TTCTACATGC AAGATGTACG	GCATGGCGCT CGTACCGCGA	GAAGGTGCTT CTTCCACGAA
11501	ACCTTGAGCG TGGAACTCGC	ACGACCTGGG TGCTGGACCC	CGTTTATCGC GCAAATAGCG	AACGAGCGCA TTGCTCGCGT	TCCACAAGGC AGGTGTTCCG
11551	CGTGAGCGTG GCACTCGCAC	AGCGGGCGGC TCGGCCGCG	GCGAGCTCAG CGCTCGAGTC	CGACCGCGAG GCTGGCGCTC	CTGATGCACA GACTACGTGT
11601	GCCTGCAAA GCGACGTTTC	GGCCCTGGCT CCGGGACCGA	GGCAGGGCA CCGTGCCCGT	GCGCGCATAG CGCCGCTATC	AGAGGCCGAG TCTCCGGCTC
11651	TCCTACTTTG AGGATGAAAC	ACGGGGCGCG TGCGCCCGCG	TGACCTGCGC ACTGGACGCG	TGGGCCCCAA ACCCGGGGTT	GCGCAGCGCG CGGCTCGCGG
11701	CCTGGAGGCA GGACCTCCGT	GCTGGGGCCG CGACCCGGG	GACCTGGGCT CTGGACCCGA	GGCGGTGGCA CCGCCACCGT	CCCGCGCGCG GGCGCGCGCG
11751	CTGGCAACGT GACCGTTGCA	CGGGCGCGTG GCCGCCGCAC	GAGGAATATG CTCCTTATAC	ACGAGGACGA TGCTCTGTCT	TGAGTACGAG ACTCATGCTC
11801	CCAGAGGACG GGTCTCCTGC	GCGAGTACTA CGCTCATGAT	AGCGGTGATG TCGCCACTAC	TTTCTGATCA AAAGACTAGT	GATGATGCAA CTACTACGTT

FIG.9A-14

23/70

11851 GACGCAACGG ACCCGGCGGT GCGGGCGGCG CTGCAGAGCC AGCGTCCGG  
 CTGCGTTGCC TGGGCGGCCA CGCCGCGCG GACGTCTCGG TCGCGAGGCC  
 11901 CCTTAACTCC ACGGACGACT GCGGCCAGGT CATGGACCGC ATCATGTGCG  
 GGAATTGAGG TGCCTGCTGA CCGCGGTCCA GTACCTGGCG TAGTACAGCG  
 11951 TGACTGCGCG CAATCCTGAC GCGTTCGCGC AGCAGCGGCA GGGCAACCGG  
 ACTGACGCGC GTTAGGACTG CGCAAGGCCG TCGTCGGCGT CCGGTTGGCC  
 12001 CTCTCCGCAA TTCTGGAAGC GGTGGTCCCG GCGCGCGCAA ACCCCACGCA  
 GAGAGGCGTT AAGACCTTCG CCACCAGGGC CGCGCGCGTT TGGGTGCGT  
 12051 CGAGAAGGTG CTGGCGATCG TAAACGCGCT GGCCGAAAC AGGGCCATCC  
 GCTCTTCAC GACCCTAGC ATTTGCGCA CCGCTTTTG TCCCGTAGG  
 12101 GGCCCGACGA GCGCGGCTG GTCTACGACG CGCTGCTTCA GCGGTGGCT  
 CCGGGCTGCT CCGCCGGAC CAGATGCTGC GCGACGAAGT CCGCACCGA  
 12151 CGTTACAACA GCGCAACGT GCAGACCAAC CTGGACCGGC TGGTGGGGGA  
 GCAATGTTGT CCGCGTTGCA CGTCTGGTTG GACCTGGCCG ACCACCCCT  
 12201 TGTGCGCGAG GCGTGCGCG AGCGTGAGCG GCGCGACGAG CAGGGCAACC  
 ACACGCGCTC CGCACCGCG TCGACTCGC GCGGTCGTC GTCCCGTTGG  
 12251 TGGGCTCCAT GGTGCACTA AACGCCTTCC TGAGTACACA GCCCGCAAC  
 ACCCGAGGTA CCAACGTGAT TTGCGGAAG ACTCATGTGT CCGCGGTTG  
 12301 GTGCCGCGGG GACAGGAGGA CTACACCAAC TTTGTGAGCG CACTGCGGCT  
 CACGCGCCC CTGTCTCCT GATGTGGTTG AAACACTCGC GTGACGCCGA  
 12351 AATGGTGACT GAGACACCG AAAGTGAGGT GTACCAGTCT GGGCCAGACT  
 TTACCACTGA CTCTGTGCG TTTCACTCCA CATGGTCAGA CCCGCTCTGA  
 12401 ATTTTTTCCA GACCAGTAGA CAAGGCTGCG AGACCGTAAA CCTGAGCCAG  
 TAAAAAGGT CTGTCATCT GTTCCGACG TCTGGCATT GGACTCGTC  
 12451 GCTTTCAAAA ACTTGCAAGG GCTGTGGGGG GTGCGGGCTC CCACAGGCGA  
 GAAAGTTTT TGAACGTCCC CGACACCCCC CACGCCGAG GGTGTCGCT  
 12501 CCGCGCGACC GTGTCTAGCT TGCTGACGCC CAACTCGCGC CTGTTGCTGC  
 GCGCGCTGG CACAGATCGA ACGACTGCGG GTTGAGCGCG GACAACGAG  
 12551 TGCTAATAGC GCCCTTACG GACAGTGSCA GCGTGTCCCG GGACACATAC  
 ACGATTATCG CGGGAAGTGC CTGTACCGT CCGACAGGGC CCTGTGTATG  
 12601 CTAGGTCACT TGCTGACACT GTACCGCGAG GCCATAGGTC AGGCGCATGT  
 GATCAAGTGA ACGACTGTGA CATGCGCTC CGGTATCCAG TCCGCGTACA  
 12651 GGACGAGCAT ACTTTCCAGG AGATTACAAG TGTAGCCGC GCGCTGGGGC  
 CCTGCTCGTA TGAAGGTCC TCTAATGTTT ACAGTCGGCG CCGACCCCG

FIG.9A-15

24/70

12701 AGGAGGACAC GGGCAGCCTG GAGGCAACCC TAAACTACCT GCTGACCAAC  
 TCCCTCTGTG CCCGTCGGAC CTCCTGTGGG ATTTGATGGA CGACTGGTTG  
 12751 CGGCGGCAGA AGATCCCCTC GTTGACAGT TTAACAGCG AGGAGGAGCG  
 GCCCGCTCT TCTAGGGGAG CAACGTGTCA AATTGTGCG TCCTCTCTCG  
 12801 CATTTTGCAG TACGTGCAGC AGAGCGTGAG CCTTAACCTG ATGCGCGAGC  
 GTAAACGCG ATGCACGTGC TCTCGCACTC GGAATTGGAC TACGCGCTGC  
 12851 GGGTAACGCC CAGCGTGGCG CTGGACATGA CCGCGCGCAA CATGSAACCG  
 CCCATTGCGG GTCGACCCG GACCTGTACT GCGCGCGCTT GTACCTTGGC  
 12901 GGCATGTATG CCTCAAACCG GCCGTTTATC AACCGCCTAA TGGACTACTT  
 CCGTACATAC GGAGTTTGGC CGGCAAAATG TTGGCGGATT ACCTGATGAA  
 12951 GCATCGCGCG GCCGCGGTGA ACCCCGAGTA TTTCACCAAT GCCATCTTGA  
 CGTAGCGCGC CGCGGCACT TGGGGCTCAT AAAGTGGTTA CGGTAGAAT  
 13001 ACCCGCACTG GCTACCGCCC CTGTGTTTCT ACACCGGGGG ATTCGAGGTG  
 TGGCGGTGAC CGATGGCGGG GGACCAAGA TGTGGCCCC TAAGCTCCAC  
 13051 CCCGAGGGA ACGATGGATT CCTCTGGGAC GACATAGACG ACAGCGTGTT  
 GGGCTCCCAT TGCTACCTAA GGAGACCCGT CTGTATCTGC TGTGCGACAA  
 13101 TTCCCCGCAA CCGCAGACCC TGCTAGAGTT GCAACAGCGC GAGCAGGCAG  
 AAGGGGCGTT GCGTCTGGG ACATCTCAA CGTTGTCGCG CTCGTCCGTC  
 13151 AGGCGGCGCT GCGAAAGGAA AGCTTCCGCA GGCCAAGCAG CTTGTCCGAT  
 TCCGCCGCGA CGCTTTCCTT TCGAAGGCGT CCGGTTCTGC GAACAGGCTA  
 13201 CTAGGCGCTG CGGCCCCGCG GTCAGATGCT AGTAGCCAT TTCCAAGCTT  
 GATCCGCGAC GCCGGGGCGC CAGTCTACGA TCATCGGGA AAGGTTCCGAA  
 13251 GATAGGGTCT CTTACAGCA CTCGACCCAC CCGCCGCGC CTGCTGGGCG  
 CTATCCAGA GAATGGTCTG GAGCGTGGTG GCGGGGCGCG GACGACCCGC  
 13301 AGGAGGAGTA CCTAAACAAC TCCTGCTGTC AGCGCAGCGC CGAAAAAAC  
 CTCCTCAT GGATTTGTGG AGCGACGACG TCGGCGTCGC GCTTTTTTGTG  
 13351 CTGCTCCGG CATTTCCCAA CAACGGGATA GAGAGCCTAG TGGACAAGAT  
 GACGAGGGCC GTAAAGGTT GTTGCCCTAT CTCTCGATC ACCTGTTCTA  
 13401 GAGTAGATGG AAGACGTACG CGCAGGAGCA CAGGACGTG CCAGGCCCGC  
 CTCATCTACC TTCTGCATGC GCGTCTCGT GTCCCTGCAC GGTCCGGGCG  
 13451 GCCCGCCAC CCGTCGTCAA AGGCACGACC GTCAGCGGGG TCTGTTGTGG  
 CGGGCGGGT GGCAGCAGTT TCCGTGCTGG CAGTCGCCCC AGACCACACC  
 13501 GAGGACGATG ACTCGGCAGA CGACAGCAGC GTCCTGGATT TGGGAGGGAG  
 CTCCTGCTAC TGAGCCGTCT GCTGTCGTCG CAGGACCTAA ACCCTCCCTC

FIG.9A-16

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13551 TGGCAACCCG TTTGCGCACC TTCGCCCAG GCTGGGGAGA ATGTTTTAAA  
 ACCGTTGGGC AAACGCGTGG AAGCGGGGTC CGACCCCTCT TACAAAAATT  
 13601 AAAAAAAAAA GCATGATGCA AAATAAAAAA CTCACCAAGG CCATGGCACC  
 TTTTTTTTTT CGTACTACGT TTTATTTTTT GAGTGGTTCC GGTACCGTGG  
 13651 GAGCGTTGGT TTTCTGTAT TCCCCTTAGT ATGCGGCGCG CGCGATGTA  
 CTCGCAACCA AAAGAACATA AGGGGAATCA TACGCCGCGC GCCGCTACAT  
 13701 TGAGGAAGGT CCTCCTCCCT CTACGAGAG TGTGGTGAGC GCGCGCCAG  
 ACTCCTTCCA GGAGGAGGGA GGATGCTCTC ACACCACTCG CGCCGCGGTC  
 13751 TGGCGGCGGC GCTGGGTCTT CCCTTCGATG CTCCCTGGA CCCGCCGTTT  
 ACCGCCGCCG CGACCCAAGA GGAAGCTAC GAGGGGACCT GGGCGGCAAA  
 13801 GTGCCCTCCG GGTACCTGCG GCCTACCGGG GGGAGAAACA GCATCCGTTA  
 CACGGAGGCG CCATGGACGC CGATGGGCC CCCTCTTTGT CGTAGGCAAT  
 13851 CTCTGAGTTG GCACCCCTAT TCGACACCAC CCGTGTGTAC CTGGTGGACA  
 GAGACTCAAC CGTGGGGATA AGCTGTGGTG GGCACACATG GACCACCTGT  
 13901 ACAAGTCAAC GGATGTGGCA TCCCTGAAC ACCAGAACGA CCACAGCAAC  
 TGTTCAAGTG CCTACACCGT AGGGACTTGA TGGTCTTGCT GGTGTCGTTG  
 13951 TTTCTGACCA CGGTCAATTA AAACAATGAC TACAGCCGG GGGAGGCAAG  
 AAAGACTGGT GCCAGTAAGT TTTGTTACTG ATGTCGGGCC CCTCCGTTT  
 14001 CACACAGACC ATCAATCTTG ACGACCGGTC GCACTGGGGC GGCACCTGA  
 GTGTGTCTGG TAGTTAGAAC TGCTGGCCAG CGTGACCCCG CCGTGGACT  
 14051 AAACATCCT GCATACCAAC ATGCCAAATG TGAACGAGTT CATGTTTACC  
 TTTGGTAGGA CGTATGGTTG TACGGTTTAC ACTTGCTCAA GTACAAATGG  
 14101 AATAAGTTTA AGGCGCGGGT GATGGTGTCT CGCTTGCCCTA CTAAGSACAA  
 TTATTTCAAT TCCGCGCCCA CTACCACAGC GCGAACGGAT GATTCTCTGT  
 14151 TCAGGTGGAG CTGAAATACG AGTGGGTGGA GTTCACGCTG CCCGAGGGCA  
 AGTCCACCTC GACTTTATGC TCACCACCTC CAAGTGCGAC GGGCTCCCGT  
 14201 ACTACTCCGA GACCATGACC ATAGACCTTA TGAACAACGC GATCGTGGAG  
 TGATGAGGCT CTGGTACTGG TATCTGAAT ACTTGTTGCG CTAGCACCTC  
 14251 CACTACTTGA AAGTGGGCAG ACAGAACGGG GTTCTGGAAA GCGACATCGG  
 GTGATGAAC TTCACCCGTC TGTCTTGCCC CAAGACCTTT CGCTGTAGCC  
 14301 GGTAAAGTTT GACACCCGCA ACTTCAGACT GGGGTTTGAC CCCGCTCACTG  
 CCAATTTCAA CTGTGGGCGT TGAAGTCTGA CCCAAACTG GGGCAGTGAC  
 14351 GTCTTGTCAT GCCTGGGGTA TATACAAACG AAGCCTTCCA TCCAGACATC  
 CAGAACAGTA CGGACCCCAT ATATGTTTGC TTCGGAAGGT AGGTCTGTAG

FIG.9A-17

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14401 ATTTTGCTGC CAGGATGCGG GGTGGACTTC ACCCACAGCC GCCTGAGCAA  
 TAAACGACG GTCTACGCC CCACCTGAAG TGGGTGTCGG CGGACTCGTT  
 14451 CTTGTTGGGC ATCCGCAAGC GGCAACCTT CCAGGAGGGC TTTAGGATCA  
 GAACAACCG TAGGCGTTCC CGTTGGGAA GGTCTCCCG AAATCCTAGT  
 14501 CCTACGATGA TCTGGAGGGT GGTAACTTC CCGCACTGTT GGATGTGGAC  
 GGATGCTACT AGACCTCCA CCATTGTAAG GCGTGACAA CCTACACCTG  
 14551 GCCTACCAGG CGAGCTTGAA AGATGACACC GAACAGGGCG GGGGTGGCGC  
 CGGATGGTCC GCTGAACTT TCTACTGTGG CTGTCCCGC CCCACCGCGG  
 14601 AGGCGGCAGC AACAGCAGTG GCAGCGGCGC GGAAGAGAAC TCCAACGCGG  
 TCCGCCGTCC TTGTCTCAC CGTCGCCGCG CCTTCTCTTG AGGTGCGCC  
 14651 CAGCCGCGGC AATGCAGCCG GTGGAGGACA TGAACGATCA TGCCATTTCG  
 GTCGGCGCCG TTACGTCCGC CACCTCCTGT ACTTGTAGT ACGGTAAGCG  
 14701 GGCGACACCT TTGCCACAGC GGCTGAGGAG AAGCGCGCTG AGGCGAAGC  
 CCGCTGTGGA AACGGTGTG CCGACTCCTC TTCGCGGAC TCCGCCCTCG  
 14751 AGCGGCCGAA GCTGCCGCC CCGCTGCGCA ACCCGAGGTC GAGAAGCCTC  
 TCGCCGGCTT CGACGGCGGG GCGCAGCGGT TGGGCTCCAG CTCTTCGGAG  
 14801 AGAAGAAACC GGTGATCAAA CCCCTGACAG AGGACAGCAA GAAACGAGT  
 TCTTCTTTGG CCACTAGTTT GGGGACTGTC TCCTGTCTT CTTTGCCTCA  
 14851 TACAACCTAA TAAGCAATGA CAGCACCTTC ACCCAGTACC GCAGCTGGTA  
 ATGTTGATT ATTCTGTTACT GTGCTGGAAG TGGTGCATGG CGTCGACCAT  
 14901 CTTGCATAC AACTACGGCG ACCCTCAGAC CGGAATCCGC TCATGACCC  
 GGAACGTATG TTGATGCCG TGGGAGTCTG GCCTTAGGCG AGTACCTGGG  
 14951 TGCTTTGCAC TCCTGACGTA ACCTGCGGCT CGGAGCAGGT CTACTGGTGC  
 ACGAAACGTG AGGACTGCAT TGGAGCCGA GCCTCGTCCA GATGACGACG  
 15001 TTGCCAGACA TGATGCAAGA CCCCCTGACC TTCCGCTCCA CGCGCCAGAT  
 AACGGTCTGT ACTACGTTCT GGGGCACTGG AAGGCGAGGT CCGCGGTCTA  
 15051 CAGCAACTTT CCGGTGGTGG GCGCCGAGCT GTTGCCCGTG CACTCCAAGA  
 GTCGTTGAAA GGCCACCACC CCGGCTCGA CAACGGGCAC GTGAGGTTCT  
 15101 GCTTCTACAA CGACCAGGCC GTCTACTCCC AACTCATCCG CCAGTTTACC  
 CGAAGATGTT GCTGGTCCGG CAGATGAGG TTGAGTAGGC GGTCAAATGG  
 15151 TCTCTGACCC ACGTGTTCAG TCGCTTTCCC GAGAACAGA TTTTGGCGCG  
 AGAGACTGGG TGCACAAGTT AGCGAAAGGG CTCTTGGTCT AAAACCGCGC  
 15201 CCCGCCAGCC CCCACCATCA CCACCGTCAG TGAACACGTT CCGTCTCTCA  
 GGGCGGTCGG GGGTGGTAGT GGTGCGAGTC ACTTTTGCAA GGACGAGAGT

FIG.9A-18

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15251 CAGATCACGG GACGCTACCG CTGCGCAACA GCATCGGAGG AGTCCAGCGA  
 GTCTAGTGCC CTGCGATGGC GACGCGTTGT CGTAGCCTCC TCAGSTCGT

15301 GTGACCATTG CTGACGCCAG ACGCCGCACC TGCCCTACG TTTACAAGGC  
 CACTGGTAAT GACTGCGGTC TCGGCGGTGG ACGGGGATGC AAATGTTCCG

15351 CCTGGGCATA GTCTCGCCGC GCGTCCTATC GAGCGCACT TTTTGAGCAA  
 GGACCCGTAT CAGAGCGGCG CGCAGGATAG CTCGGCGTGA AAAACTCGTT

15401 GCATGTCCAT CCTTATATCG CCCAGCAATA ACACAGGCTG GGGCTCGCG  
 CGTACAGGTA GGAATATAG GGGTCGTTAT TGTGTCCGAC CCCGACGCGG

15451 TTCCCAAGCA AGATGTTTGG CGGGGCCAAG AAGCGCTCCG ACCAACACCC  
 AAGGGTTTCT TCTACAAACC GCCCGGTTT TCGCGAGGC TGGTTGTGGG

15501 AGTGCGCGTG CGCGGGCACT ACCGCGCGCC CTGGGGCGCG CACAACGCG  
 TCACGCGCAC GCGCCGTGA TGCGCGCGG GACCCGCGC GTGTTTGC GC

15551 GCCGCACTGG GCGCACCACC GTGATGACG CCATCGACGC GGTGTGGAG  
 CGGCGTGACC CGCGTGGTG CAGCTACTGC GGTAGCTGCG CCACCACCTC

15601 GAGGCGCGCA ACTACACGCC CACGCCGCCA CCAAGTGTCCA CAGTGGACGC  
 CTCGCGCGT TGATGTGCGG GTGCGCGGT GGTCAAGGT GTCACTGCG

15651 GGCCATTGAG ACCGTGGTGC GCGGAGCCCG GCGCTATGCT AAAATGAAGA  
 CCGGTAAGTC TGGACACACG CGCTCGGGC GCGATACGA TTTTACTTCT

15701 GACGGCGGAG GCGCGTAGCA CGTCGCCACC GCCGCGGACC CGGCACTGCC  
 CTGCCGCTC CGCGCATCGT GCAGCGGTGG CGCGGCTGG GCCGTGACGG

15751 GCCCAACGCG CGGCGGCGGC CCTGCTTAAC CGCGCACGTC GCACCGGCGG  
 CGGGTTGCGC GCCGCCGCCG GGACGAATTG GCGGTGCGAG CGTGCCGGG

15801 ACGGGCGGCC ATGCGGGCCG CTCGAAGGCT GGCGCGGGT ATTGTCACTG  
 TGCCCGCGG TACGCCCGGC GAGCTTCCGA CGCGGCCCA TAACAGTAGC

15851 TGCCCCCAG GTCCAGGCGA CGAGCGGCG CGCAGCAGC CGCGGCCATT  
 ACGGGGGTC CAGGTCCGCT GCTCGCGGC GCGTCTGTC GCGCGGTAA

15901 AGTGCTATGA CTCAGGGTCG CAGGGCAAC GTGTATTGGG TGCAGACTC  
 TCACGATACT GAGTCCAGC GTCCCGTTG CACATAACCC ACGCGCTGAG

15951 GGTTAGCGGC CTGCGCGTGC CGGTGCGCAC CGCCCCCG CGCAACTAGA  
 CCAATGCCG GACGCGCACG GGCACGCGTG GCGGGGGG GCGTTGATCT

16001 TTGCAAGAAA AAATACTTA GACTCGTACT GTTGATGTA TCCAGCGCGC  
 AACGTTCTTT TTGATGAAT CTGAGCATGA CAACATACAT AGGTGCGCGC

16051 GCGGCGCGCA ACGAAGCTAT GTCCAAGCGC AAAATCAAAG AAGAGATGCT  
 CGCCGCGCGT TGCTTCGATA CAGGTTGCGG TTTTAGTTTC TTCTCTACGA

FIG.9A-19

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16101 CCAGGTGATC GCGCCGGAGA TCTATGGCCC CCCGAAGAAG GAAGAGCAGG  
 GGTCCAGTAG CGCGGCCTCT AGATACCGGG GGGCTTCTTC CTTCGCTCC

16151 ATTACAAGCC CCGAAAGCTA AAGCGGGTCA AAAAGAAAAA GAAAGATGAT  
 TAATGTTCCG GGCCTTTCGAT TTGCGCCAGT TTTTCTTTTT CTTTTACTA

16201 GATGATGAAC TTGACGACGA GGTGGAACGT CTGCACGCTA CCGCGCCAG  
 CTACTACTTG AACTGCTGCT CCACCTTGAC GACGTGCGAT GGC CGCGGGTC

16251 GCGACGGGTA CAGTGGAAG GTGACGCGT AAAACGTGTT TTGCGACCCG  
 CGCTGCCCAT GTCACCTTTC CAGCTGCGCA TTTTGCACAA AACGCTGGGC

16301 GCACCACCGT AGTCTTTACG CCCGGTGAGC GCTCCACCCG CACCTACAAG  
 CGTGGTGGCA TCAGAAATGC GGGCCACTCG CGAGGTGGGC GTGAGTGTC

16351 CGCGTGTATG ATGAGGTGTA CGCGACGAG GACCTGCTTG AGCAGGCCAA  
 GCGCACATAC TACTCCACAT GCGCTGCTC CTGGACGAAC TCGTCCGGTT

16401 CGAGCGCCTC GGGGAGTTTG CCTACGGAAA GCGGCATAAG GACATGCTGG  
 GCTCGCGGAG CCCCTCAAAC GGATGCCCTT CGCCGTATTC CTGTACGACC

16451 CGTTGCGCCT GGACGAGGGC AACCACACAC CTAGCCTAAA GCCCGTAACA  
 GCAACGGCGA CTGCTCCCG TTGGTTGTG GATCGATT TT GGGCATTGT

16501 CTGCAGCAGG TGCTGCCCGC GCTTGACCG TCCGAAGAAA AGCGCGCCT  
 GACGTCGTCC ACGACGGGC CGAACGTGGC AGGCTTCTTT TCGCGCCGA

16551 AAAGCGCGAG TCTGTTGACT TGGACCCAC CGTGACGTG ATGGTACCCA  
 TTTGCGCTC AGACCACTGA ACCGTGGGTG GCACGTCGAC TACCATGGGT

16601 AGCGCCAGCG ACTGGAAGAT GTCTTGAAAA AAATGACCGT GGAACCTGGG  
 TCGCGCTCGC TGACCTCTTA CAGAACCTTT TTTACTGGCA CTTTGAGCC

16651 CTGAGCCCG AGGTCCGCGT GCGGCCAATC AAGCAGGTGG CGCCGGGACT  
 GACCTCGGGC TCCAGGCGCA CGCGGTTAG TTGCTCCACC GCGGCCCTGA

16701 GGGCGTGCAG ACCGTGGACG TTCAGATACC CACTACCACT AGCACCAGTA  
 CCCGACGTC TGGCACTGC AAGTCTATGG GTGATGCTCA TCGTGGTCAT

16751 TTGCCACCGC CACAGAGGGC ATGGAGACAC AAACGTCCCC GGTTCGCTCA  
 AACGGTGGCG GTGTCTCCCG TACCTCTGTG ITTGAGGGG CCAACGGAGT

16801 GCGGTGGCGG ATGCCGCGGT GCAGCGGCTC GTGCGGCGG CGTCAAGAC  
 CGCCACCGCC TACGGCGCCA CGTCCGCCAG CGACGCCGCG GCAGGTTCTG

16851 CTCTACGGAG GTGCAACCG ACCCGTGGAT GTTTCGCGTT TCAGCCCCC  
 GAGATGCCCT CACGTTTGCC TGGGACCTTA CAAAGCGCAA AGTCGGGGGG

16901 GCGGCCGCGC CGGTTGAGG AAGTACGGCG CGCGCAGCG GCTACTGCC  
 CCGCGGGCGC GGCAAGCTCC TTCATGCCG GCGGTGCGG CGATGACGGG

FIG.9A-20

29/70

16951 GAATATGCC TACATCCTTC CATTGCGCCT ACCCCCGGCT ATCGTGGCTA  
 CTTATACGGG ATGTAGGAAG GTAACGCCGA TGGGGGCCGA TAGCACCGBAT

17001 CACCTACCGC CCCAGAAGAC GAGCAACTAC CCGACGCCGA ACCACCAGTG  
 GTGGATGGCG GGGTCTTCTG CTCGTTGATG GGTGCGGCT TGGTGTGTAC

17051 GAACCCGCCG CCGCCGTCGC CGTCGCCAGC CCGTGTCTGG CCGGATTTC  
 CTTGGCGGCG GCGGCCAGCG GCAGCGGTG GGCACGACCG GGGCTAAAGG

17101 GTGCGCAGGG TGGCTCGCGA AGGAGGCAGG ACCCTGGTGC TGCCAACAGC  
 CACGCGTCCC ACCGAGCGCT TCCTCCGTCC TGGGACCACG ACGGTTGTGCG

17151 GCGCTACCAC CCCAGCATCG TTTAAAGGCC GGTCTTTGTG GTTCTTGCA  
 CGCGATGGTG GGGTCGTAGC AAATTTTCGG CCAGAAACAC CAAGAAGCTC

17201 ATATGGCCCT CACCTGCCGC CTCGTTTCC CGGTGCCGGG ATTCGAGGA  
 TATACGGGA GTGGACGGCG GAGGCAAAAG GCCACGGCCC TAAGGCTCCT

17251 AGAATGCACC GTAGGAGGGG CATGGCCGGC CACGGCTGA CGGGCGGCAT  
 TCTTACGTGG CATCTCCCC GTACCGGCG GTGCGGACT GCCCGCCGTA

17301 GCGTCGTGCG CACCACGGCG GCGGCGCGCG GTGCGACCGT CGCATGCGCG  
 CGCAGCACGC GTGGTGGCCG CCGCCGCGCG CAGCGTGGA GCGTACGCGC

17351 GCGGTATCCT GCCCTCCTT ATTCCAATGA TCGCCGCGGC GATTGGCGCC  
 CGCCATAGGA CGGGGAGGAA TAAGGTGACT AGCGGCGCGC CTAACCGCGG

17401 GTGCCCGGAA TTGCATCCGT GGCCCTTGCA GCGCAGAGAC ACTGATTAA  
 CACGGGCTT AACGTAGGCA CCGGAACGTC CGCGTCTCTG TGAATAATT

17451 AACAAATTGC ATGTGGAAAA ATCAAAATAA AAAGTCTGGA CTCTCACGCT  
 TTGTTCAACG TACACCTTTT TAGTTTTATT TTTCAGACCT GAGAGTGCAG

17501 CGCTTGGTCC TGTAACATATT TTGTAGAATG GAAGACATCA ACTTTGCGTC  
 GCGAACAGG ACATTGATAA AACATCTTAC CTTCTGTAGT TGAACGCGAG

17551 TCTGGCCCCG CGACACGGCT CGCGCCGTT CATGGGAAAC TGGCAAGATA  
 AGACCGGGCG GCTGTGCCGA GCGCGGGCAA GTACCCTTTG ACCGTTCTAT

17601 TCGGCACCA GCAATATGAGC GGTGGCGCCT TCAGCTGGGG CTCGCTGTGG  
 AGCGGTGGTC GTTATACTCG CCACCGCGGA AGTCGACCCC GAGCGACACC

17651 AGCGGCATTA AAAATTTCGG TTCCACCGTT AAGAACTATG GCAGCAAGGC  
 TCGCCGTAAT TTTTAAAGCC AAGGTGGCAA TTCTTGATAC CGTCGTTCCG

17701 CTGGAACAGC AGCAGAGGCC AGATGCTGAG GGATAAGTTG AAAGAGCAAA  
 GACCTGTGCG TCGTGTCCGG TCTACGACT CCTATTCAAC TTCTCGTTT

17751 ATTTCCAACA AAAGGTGGTA GATGGCCTGG CCTCTGGCAT TAGCGGGGTG  
 TAAAGGTTGT TTTCACCAT CTACCGGACC GGAGACCGTA ATCGCCCCAC

FIG.9A-21

30/70

17801 GTGGACCTGG CCAACCAGGC AGTGCAAAAT AAGATTAACA GTAAGCTTGA  
 CACCTGGACC GGTGTGTCGG TCACGTTTTA TTCTAATTGT CATTCGAACT  
 17851 TCCCCGCCCT CCCGTAGAGG AGCCTCCACC GGCCGTGGAG ACAGTGTCTC  
 AGGGGCGGGA GGGCATCTCC TCGGAGGTGG CCGGCACCTC TGTACACAGG  
 17901 CAGAGGGGCG TGGCGAAAAG CGTCCGCGCC CCGACAGGGA AGAAACTCTG  
 GTCTCCCCGC ACCGCTTTTC GCAGGCGCGG GCCTGTCCCT TCTTTGAGAC  
 17951 GTGACGCAAA TAGACGAGCC TCCCTCGTAC GAGGAGGCAC TAAAGCAAGG  
 CACTGCGTTT ATCTGCTCGG AGGGAGCATG CTCTCCGCTG ATTTGCTTCC  
 18001 CCTGCCACC ACCCGTCCA TCGCGCCCAT GGCTACCGGA GTGCTGGGCC  
 GGACGGGTGG TGGCAGGGT AGCGCGGTA CCGATGGCTC CACGACCCGG  
 18051 AGCACACACC CGTAACGCTG GACCTGCCTC CCCCCGCCGA CACCGAGCAG  
 TCGTGTGTGG GCATTGCGAC CTGGACGGAG GGGGCGGCTC GTGGTGCTC  
 18101 AAACCTGTGC TGCAGGCCC GACCGCGCTT GTTGTAACCC GTCTAGCCG  
 TTTGGACAGC ACGGTCCGGG CTGGCGGCAA CAACATTGGG CAGGATCGGC  
 18151 CGCGTCCCTG CGCGCGCCG CCAGCGGTCC GCGATCGTTG CGGCCGTAG  
 GCGACGGGAC GCGGCGCGG GGTCCGCCAG GCCTAGCAAC GCCGGGCATC  
 18201 CCAGTGGCAA CTGGCAAAGC ACGTGAACA GCATCGTGGG TCTGGGGGTG  
 GGTACCCGTT GACCGTTTCG TGTGACTTGT CGTAGCACC AGACCCCCAC  
 18251 CAATCCCTGA AGCGCCGACG ATGCTTCTGA TAGCTAACGT GTCGTATGTG  
 GTTAGGGACT TCGCGGCTGC TACGAAGACT ATCGATTGCA CAGCATACAC  
 18301 TGTATGTAT GCGTCCATGT CGCCGCCAGA GGAGCTGCTG AGCCGCCGCG  
 ACAGTACATA CGCAGGTACA GCGGCGGTCT CCTCGACGAC TCGGCGGCGC  
 18351 CGCCCGCTTT CCAAGATGGC TACCCCTTCG ATGATGCCCG AGTGGTCTTA  
 GCGGGCGAAA GTTCTACCG ATGGGGAAGC TACTACGGCG TCACCAAGAT  
 18401 CATGCACATC TCGGGCCAGG ACGCCTCGGA GTACCTGAGC CCCGGCTGG  
 GTACGTGTAG AGCCCGGTCC CATGGACTCG GGGCCGACC  
 18451 TGCAGTTTGC CCGCGCCACC GAGACGTACT TCAGCCTGAA TAACAAGTTT  
 ACGTCAAACG GCGCGGTTGG CTCTGCATGA AGTCGGACTT ATTGTTCAAA  
 18501 AGAAACCCCA CGGTGGCGCC TACGCACGAC GTGACCACAG ACCGGTCCCA  
 TCTTTGGGGT GCCACC GCGG ATGCGTGTCT CACTGGTGTG TGGCCAGGGT  
 18551 GCGTTTGACG CTGCGGTTCA TCCCTGTGGA CCGTGAGGAT ACTGCGTACT  
 CGAAACTGC GACGCCAAGT AGGGACACCT GGCACCTCTA TGACGCATGA  
 18601 CGTACAAGGC GCGGTTACCC CTAGCTGTGG GTGATAACCG TGTGCTGGAC  
 GCATGTTCCG GCCCAAGTGG GATCGACACC CACTATTGGC ACACGACCTG

FIG.9A-22

31/70

18651 ATGGCTTCCA CGTACTTTGA CATCCGCGGC GTGCTGGACA GGGGCCCTAC  
 TACCGAAGGT GCATGAAACT GTAGGCGCCG CACGACCTGT CCCCGGGATG  
 18701 TTTTAAGCCC TACTCTGGCA CTGCCTACAA CGCCCTGGCT CCCAAGGGTG  
 AAAATTCGGG ATGAGACCGT GACGGATGTT GCGGGACCGA GGGTTCCCAAC  
 18751 CCCCAAATCC TTGCGAATGG GATGAAGCTG CTACTGCTCT TGAAATAAAC  
 GGGGTTTAGG AACGCTTACC CTACTTCGAC GATGACGAGA ACTTTATTTG  
 18801 CTAGAAGAAG AGGACGATGA CAACGAAGAC GAAGTAGACG AGCAAGCTGA  
 GATCTTCTTC TCCTGCTACT GTTGCTTCTG CTTCACTGCG TCGTTTCGACT  
 18851 GCAGCAAAAA ACTCACGTAT TTGGGCAGGC GCCTTATTCT GGTATAAATA  
 CGTCGTTTTT TGAGTGCATA AACCCGTCCG CGGAATAAGA CCATATTTAT  
 18901 TTACAAAGGA GGGTATTCAA ATAGGTGTCTG AAGGTCAAAC ACCTAAATAT  
 AATGTTTCTC CCATAAGTT TATCCACAGC TTCCAGTTTG TGGATTATATA  
 18951 GCCGATAAAA CATTTC AACCTCAA ATAGGAGAAT CTCAGTGATA  
 CGGCTATTTT GTAAAGTTGG ACTTGGAGTT TATCCTCTTA GAGTCACCAT  
 19001 CGAAACAGAA ATTAATCATG CAGCTGGGAG AGTCTAAAA AAGACTACCC  
 GCTTTGTCTT TAATTAGTAC GTCGACCCCTC TCAGGATTTT TTCTGATGGG  
 19051 CAATGAAACC ATGTTACGGT TCATATGCAA AACCCACAAA TGAAAATGGA  
 GTTACTTTGG TACAATGCCA AGTATACGTT TTGGGTGTTT ACTTTTACCT  
 19101 GGGCAAGGCA TTCTTGTAAG GCAACAAAAT GGAAAGCTAG AAAGTCAAGT  
 CCCGTTCCGT AAGAACATTT CGTTGTTTTA CCTTTCGATC TTTCAGTTCA  
 19151 GGAAATGCAA TTTTCTCAA CTACTGAGGC AGCCGAGGC AATGGTGATA  
 CCTTTACGTT AAAAAGAGTT GATGACTCCG TCGCGTCCG TTACCACTAT  
 19201 ACTTGACTCC TAAAGTGGA TTGTACAGTG AAGATGTAGA TATAGAAACC  
 TGAAGTGGG ATTTACCAT AACATGTAC TTCTACATCT ATATCTTTGG  
 19251 CCAGACACTC ATATTTCTTA CATGCCCACT ATTAAGGAAG GTAACTCAGG  
 GTCTGTGAG TATAAGAAT GTACGGGTGA TAATTCCTTC CATTGAGTGC  
 19301 AGAACTAATG GGCCAAACAAT CTATGCCCAA CAGGCCTAAT TACATTGCTT  
 TCTTGATTAC CCGGTGTGTA GATACGGGTT GTCCGGATTA ATGTAACGAA  
 19351 TTAGGGACAA TTTTATTGGT CTAATGTATT ACAACAGCAC GGGTAATATG  
 AATCCCTGTT AAAATAACCA GATTACATAA TGTTGTCTGT CCCATTATAC  
 19401 GGTGTTCTGG CGGGCCAAGC ATCGCAGTTG AATGCTGTGG TAGATTGCA  
 CCACAAGACC GCCCGGTTCC TAGCGTCAAC TTACGACAAC ATCTAAACGT  
 19451 AGACAGAAAC ACAGAGCTTT CATACCAGCT TTTGCTTGAT TCCATTGGTG  
 TCTGCTTTTG TGTCGAGAAA GTATGGTCGA AAACGAACATA AGGTAACCCAC

FIG.9A-23

32/70

19501 ATAGAACCCAG GTACTTTTCT ATGTGGAATC AGGCTGTTGA CAGCTATGAT  
 TATCTTGGTC CATGAAAAGA TACACCTTAG TCCGACAACT GTGCATACTA  
 19551 CCAGATGTTA GAATTATTGA AAATCATGGA ACTGAAGATG AACTTCCAAA  
 GGTCTACAAT CTTAATAACT TTTAGTACCT TGACTTCTAC TTGAAGGTTT  
 19601 TTACTGCTTT CCACTGGGAG GTGTGATTAA TACAGAGACT CTTACCAAGG  
 AATGACGAAA GGTGACCCTC CACACTAATT ATGTCTCTGA GAATGTTTCC  
 19651 TAAACCTAA AACAGGTCAG GAAATGGAT GGGAAAAAGA TGCTACAGAA  
 ATTTTGGATT TTGTCCAGTC CTTTACCTA CCGTTTTTCT ACGATGTCTT  
 19701 TTTTCAGATA AAAATGAAAT AAGAGTTGGA AATAATTTTG CCATGGAAT  
 AAAAGTCTAT TTTTACTTTA TTCTCAACCT TTATTAAGAC GGTACCTTTA  
 19751 CAATCTAAAT GCCAACCTGT GGAGAAATTT CCTGTACTCC AACATAGCGC  
 GTTAGATTTA CGGTTGGACA CCTCTTTAAA GGACATGAGG TTGTATCGCG  
 19801 TGTATTGGCC CGACAAGCTA AAGTACAGTC CTTCCAACGT AAAAATTTCT  
 ACATAAACGG GCTGTTGAT TTCTATGTCAG GAAGTTTGCA TTTTAAAGA  
 19851 GATAACCCAA ACACCTACGA CTACATGAAC AAGCGAGTGG TGCTCCCGG  
 CTATTGGGTT TGTGGATGCT GATGTACTTG TTCGCTCACC ACCGAGGGCC  
 19901 GCTAGTGGAC TGCTACATTA ACCTTGGAGC ACGCTGGTCC CTTGACTATA  
 CGATCACCTG ACGATGTAAT TGGAACCTCG TCGCACCAGG GAACTGATAT  
 19951 TGGACAACGT CAACCCATTT AACCACCACC GCAATGCTGG CCTGCGCTAC  
 ACCTGTTGCA GTTGGGTAAA TTGGTGGTGG CGTTACGACC GGACGCGATG  
 20001 CGCTCAATGT TGCTGGGCAA TGGTCGCTAT GTGCCCTTCC ACATCCAGGT  
 GCGAGTTACA ACGACCCGTT ACCAGCGATA CACGGGAAGG TGTAGTGCCA  
 20051 GCCTCAGAAG TTCTTTGCCA TTA AAAACCT CTTCTCCTG CCGGGCTCAT  
 CGGAGTCTTC AAGAAACGGT AATTTTTTGA GGAAGAGGAC GGCCGAGTA  
 20101 ACACCTACGA GTGGAATTC AGGAAGGATG TTAACATGGT TCTGCAGAGC  
 TGTGGATGCT CACCTTGAAG TCCTTCCTAC AATTGTACCA AGACGTCTCG  
 20151 TCCCTAGGAA ATGACCTAAG GGTGTGACGA GCCAGCATT AAGTTTGATAG  
 AGGATCCTT TACTGGATTC CCAACTGCCT CGGTGTAAT TCAACTATC  
 20201 CATTTGCTTT TACGCCACCT TCTTCCCAT GGGCCACAAC ACCGCTCCCA  
 GTAAACGGAA ATGCGGTGGA AGAAGGGTA CCGGGTGTG TGCGGGAGGT  
 20251 CGCTTGAGGC CATGCTTAGA AACGACACCA ACGACCACTG CTTTAAACGAC  
 GCGAACTCCG GTACGAATCT TTGCTGTGGT TGCTGGTCAG GAAATTTGCTG  
 20301 TATCTCTCCG CCGCCAACAT GCTCTACCCT ATACCCGCCA ACGCTACCAA  
 ATAGAGAGGC GCGGTTGTA CGAGATGGGA TATGGCGGT TGCGATGGTT

FIG.9A-24

## 33/70

20351 CGTGCCCAT TCCATCCCTC CCCGCACTG GCGGCTTTC GCGGGCTGGG  
 GCACGGGTAT AGGTAGGGGA GGGCGTTGAC CCGCCGAAAG GCGCCGACCC  
 20401 CCTTCACGGC CCTTAAGACT AAGGAAACCC CATCACTGGG CTCGGGCTAC  
 GGAAGTGC GC GGAATTCTGA TTCCTTTGGG GTAGTGACCC GAGCCCGATG  
 20451 GACCCTTATT ACACCTACTC TGGCTCTATA CCCTACCTAG ATGGAACCTT  
 CTGGGAATAA TGTGGATGAG ACCGAGATAT GGGATGGATC TACCTTGGAA  
 20501 TTACCTCAAC CACACCTTTA AGAAGGTGGC CATTACCTTT GACTCTTCTG  
 AATGGAGTTG GTGTGGAAAT TCTCCACCG GTAATGGAAA CTGAGAAGAC  
 20551 TCAGCTGGCC TGGCAATGAC CGCCTGCTTA CCCCCAACGA GTTTGAAATT  
 AGTCGACCGG ACCGTTACTG GCGGACGAAT GGGGGTTGCT CAAACTTTAA  
 20601 AAGCGCTCAG TTGACGGGGA GGGTTACAAC GTTGCCCACT GTAACATGAC  
 TTCGCGAGTC AACTGCCCTT CCAATGTTG CAACGGGTCA CATTGTACTG  
 20651 CAAAGACTGG TTCTGSGTAC AAATGCTAGC TAACTATAAC ATTGGCTACC  
 GTTTCTGACC AAGGACCATG TTTACGATCG ATTGATAATT TAACCGATGG  
 20701 AGGGCTTCTA TATCCAGAG AGCTACAAGG ACCGCATGTA CTCCTTCTTT  
 TCCCGAAGAT ATAGGGTCTC TCGATGTTCC TGGCGTACAT GAGGAAGAAA  
 20751 AGAAACTTCC AGCCCATGAG CCGTCAGGTG GTGGATGATA CTAATAACAA  
 TCTTTGAAGG TCGGGTACTC GGCAGTCCAC CACCTACTAT GATTTATGTT  
 20801 GGA CTACCAA CAGGTGGGCA TCCTACACCA ACACAACAAC TCTGGATTGG  
 CCTGATGGTT GTCCACCCGT AGGATGTGGT TGTGTTGTTG AGACCTAAAC  
 20851 TTGGCTACCT TGCCCCCACC ATGCGCGAAG GACAGGCCTA CCCTGCTAAC  
 AACCGATGGA ACGGGGGTGG TACGCCTTC CTGTCCGGAT GGGACGATTG  
 20901 TTCCCTATC CGCTTATAGG CAAGACCGCA GTTGACAGCA TTACCCAGAA  
 AAGGGGATAG GCGAATATCC GTTCTGGCGT CAACTGTGCT AATGGGTCTT  
 20951 AAAGTTTCTT TGCATCGCA CCCTTTGGCG CATCCATTTC TCCAGTAAC  
 TTCAAAGAA ACCTAGCGT GGGAAACCGC GTAGGGTAAG AGGTCAATTGA  
 21001 TTATGTCCAT GGGCGCACTC ACAGACCTGG GCCAAAACCT TCTCTACGCC  
 AATACAGGTA CCCGCGTGAG TGTCTGGACC CGGTTTTGGA AGAGATGCGG  
 21051 AACTCCGCCC ACGCGCTAGA CATGACTTTT GAGGTGGATC CCATGGACGA  
 TTGAGGCGGG TGCGCGATCT GTACTGAAAA CTCCACCTAG GGTACCTGCT  
 21101 GCCCACCTT CTTTATGTTT TGTTGAAGT CTTTGACGTG GTCCGTGTGC  
 CGGGTGGGAA GAAATACAAA ACAAACTTCA GAAACTGCAC CAGGCACACG  
 21151 ACCAGCCGCA CCGCGGGCTC ATCGAAACCG TGTACCTGCG CACGCCCTTC  
 TGTCGGCGT GCGCGCGCAG TAGCTTTGCG ACATGGACGC GTGCGGGAAG

FIG.9A-25

34/70

21201 TCGGCCGGCA AGCCACAAAC ATAAAGAAGC AAGCAACATC AACAAACAGT  
 AGCCGGCCGT TCGGTGTTG TATTTCTCG TTCTGTGTAG TTGTTGTGCA  
 21251 GCGGCCATGG GCTCCAGTGA GCAGGAAGT AAAGCCATTG TCAAGATCT  
 CGCGGTACCG CGAGGTCACT CGTCTTGAC TTTCGGTAAC AGTTTCTAGA  
 21301 TGGTTGTGGG CCATATTTT TGGGCACCTA TGACAAGCGC TTTCAGGCT  
 ACCAACACCC GGTATAAAAA ACCCGTGGAT ACTGTTCCGC AAAGGTCCGA  
 21351 TTGTTTCTCC ACACAAGCTC GCCTGCGCCA TAGTCAATAC GGCCGGTCGC  
 AACAAAGAGG TGTGTTGAG CGGACGCGGT ATCAGTTATG CCGGCCAGCG  
 21401 GAGACTGGGG GCGTACACTG GATGGCCTTT GCCTGGAACC CGCACTCAAA  
 CTCTGACCCC CGCATGTGAC CTACCGGAAA CGGACCTTGG GCGTGAGTTT  
 21451 AACATGCTAC CTCTTTGAGC CCTTTGGCTT TTCTGACCAG CGACTCAAGC  
 TTGTACGATG GAGAACTCG GGAACCGAA AAGACTGGTC GCTGAGTTCG  
 21501 AGGTTTACCA GTTTGAGTAC GAGTCACTCC TGGCCGCTAG CGCATTGCT  
 TCCAAATGGT CAAACTCATG CTCAGTGAGG ACGCGGCATC GCGGTAACGA  
 21551 TCTTCCCCCG ACCGCTGTAT AACCGTGAA AAGTCCACCC AAAGCGTACA  
 AGAAGGGGGG TGGCGACATA TTGCGACCTT TTCAGGTGGG TTTCGATGT  
 21601 GGGGCCCAAC TCGGCCGCTT GTGGACTATT CTGCTGCATG TTCTCCACG  
 CCCCGGGTTG AGCCGGCGGA CACCTGATAA GACGACGTAC AAAGAGGTGC  
 21651 CCTTTGCCAA CTGGCCCCAA ACTCCCATGG ATCACAACCC CACCATGAAC  
 GGAACGGTT GACCGGGGTT TGAGGGTACC TAGTGTGGG GTGGTACTTG  
 21701 CTTATTACCG GGGTACCCAA CTCCATGCTC AACAGTCCCC AGGTACAGCC  
 GAATAATGGC CCCATGGGTT GAGGTACGAG TTGTCAGGGG TCCATGTCCG  
 21751 CACCCTGCGT CGCAACCAAG AACAGCTCTA CAGCTTCTGT GAGCGCCACT  
 GTGGGACGCA GCGTTGGTCC TTGTCGAGAT GTCGAAGGAC CTCGCGGTGA  
 21801 CGCCCTACTT CCGCAGCCAC AGTGCGCAGA TTAGGAGCGC CACTTCTTTT  
 GCGGGATGAA GCGCTCGGTG TCACGCTCT AATCTCGCG GTGAAGAAAA  
 21851 TGTCACTTGA AAAACATGTA AAAAATATGT ACTAGAGACA CTTTCAATAA  
 ACAGTGAAC TTTTGTACAT TTTTATTACA TGATCTCTGT GAAAGTIATT  
 21901 AGGCAAAATG TTTTATTGT AACTCTCGG GTGATTATTT ACCCCACCC  
 TCCGTTTACG AAAATAAACA TGTGAGAGCC CACTAATAAA TGGGGTGGG  
 21951 TTGCGCTCTG CGCCGTITAA AAATCAAAGG GGTTCGCGG CGCATCGTA  
 AACGCGAGAC GCGGCAAAAT TTAGTTTCC CCAAGACGG CGGTAGCGAT  
 22001 TGGCCCACTG GCAGGGACAC GTTGCATAC TGGTGTTTAG TGCTCACTT  
 ACGCGGTGAC CGTCCCTGTG CAACGCTATG ACCACAATC ACGAGGTGAA

FIG.9A-26

35/70

22051 AAAC TCAGGC ACAACCATCC GCGGCAGCTC GGTGAAGTTT TCAC TCACA  
 TTTGAGTCCG GTTGGTAGG CGCGTCGAG CCAC TCAAA AGTGAGTGT  
 22101 GGTCGCGCAC CATCACCAAC GCGTTTAGCA GGTGGGGCGC CGATATCTTG  
 CCGACGCGTG GTAGTGGTTG CGCAAATCGT CCAGCCGCG GCTATAGAAC  
 22151 AAGTCGCAGT TGGGGCCTCC GCCCTGCGCG CGCGAGTTGC GATACACAGG  
 TTCAGCGTCA ACCCGGAGG CGGACGCGC GCGCTCAACG CTATGTGTCC  
 22201 GTTGACGAC TGGAACACTA TCAGCGCCGG GTGGTGCACG CTGGCCAGCA  
 CAACGTCGTG ACCTTGTGAT AGTCGCGGCC CACCACGTGC GACCGGTCTG  
 22251 CGCTCTTGTC GGAGATCAGA TCCGCGTCCA GGTCTCCGCG GTTGCTCAGG  
 GCGAGAACAG CCTCTAGTCT AGGCGCAGGT CCAGGAGGCG CAACGAGTCC  
 22301 GCGAACGGAG TCAACTTTGG TAGCTGCCTT CCAAAAAAGG GCGGTCGCC  
 CGCTTGCTC AGTTGAAACC ATCGACGGAA GGGTTTTTCC CGCGCACGGG  
 22351 AGGCTTTGAG TTGCACTCGC ACCGTAGTGG CATCAAAAGG TGACCGTGCC  
 TCCGAAACTC AACGTGAGCG TGGCATCACC GTAGTTTTCC ACTGGCACGG  
 22401 CGGTCTGGCG GTTAGGATAC AGCGCTGCA TAAAGCCTT GATCTGCTTA  
 GCCAGACCCG CAATCCTATG TCGCGAGCT ATTTTCGAA CTAGACGAAT  
 22451 AAAGCCACCT GAGCCTTTGG GCCTTCAGAG AAGAATGCG CGCAAGACTT  
 TTTCGGTGGG CTCGGAACG CGGAAGTCTC TTCTGTACG GCGTCTGAA  
 22501 GCGGGAAC TGATTGGCCG GACAGGCCGC GTCGTGCACG CAGCACCTTG  
 CGGCCTTTG ACTAACGGC CTGTCCGGCG CAGCACGTGC GTCGTGGAAC  
 22551 CGTCGGTGTG GGAGATCTGC ACCACATTTT GGGCCACCG GTTCTTCAGG  
 GCAGCCACAA CCTCTAGACG TGGTGTAAAG CCGGGGTGGC CAAGAAGTGC  
 22601 ATCTTGGCCT TGCTAGACTG CTCCTTCAGC GCGCGCTGCC CGTTTTGCGT  
 TAGAACCGGA AGATCTGAC GAGGAAGTCG GCGCGACGG GCAAAAGCGA  
 22651 CGTCACATCC ATTTCAATCA CGTGTCTCTT ATTATCATA ATGCTTCCGT  
 CAGTGTAGG TAAAGTTAGT GCACAGGAA TAAATAGTAT TACGAAGGCA  
 22701 GTAGACACTT AAGCTCGCCT TCGATCTCAG CGCAGCGGTG CAGCCACAAC  
 CATCTGTGAA TTCAGCGGA AGCTAGAGTC GGTGCGCCAC GTCGGTGTG  
 22751 GCGCAGCCCG TGGGCTCGTG ATGCTTGTAG GTCACCTCTG CAAACGACTG  
 CGCGTCGGGC ACCCGAGCAC TACGAACATC CAGTGGAGAC GTTTGCTGAC  
 22801 CAGGTACGCC TGCAGGAATC GCCCATCAT CGTCACAAAG GTCTTTGGTC  
 GTCCATGCGG ACGTCTTAG CGGGTAGTA GCAGTGTTC CAGAACAACG  
 22851 TGGTGAAGGT CAGCTGCAAC CGCGGTGCT CCTCGTTCAG CCAGGTCTTG  
 ACCACTTCCA GTCGACGTTG GCGCCACGA GGAGCAAGTC GGTCCAGAAC

FIG.9A-27

36/70

22901 CATACGGCCG CCAGAGCTTC CACTTGGTCA GGCAGTAGTT TGAAGTTCGC  
 GTATCCGGC GGTCTCGAAG GTGAACCACT CCGTCATCAA ACTTCAAGCG  
 22951 CTTTAGATCG TTATCCACGT GGTACTTGTG CATCAGCGCG CGCGCAGCCT  
 GAAATCTAGC AATAGGTGCA CCATGAACAG GTAGTCGCGC GCGCGTCGGA  
 23001 CCATGCCCTT CTCCCAGCA GACACGATCG GCACACTCAG CGGGTTCATC  
 GGTACGGGAA GAGGGTGCGT CTGTGCTAGC CGTGTGAGTC GCCCAAGTAG  
 23051 ACCGTAATTT CACTTTCGCG TTCGCTGGG TCTTCTCTTT CCTCTTGGCT  
 TGCATTAAA GTGAAAGGCG AAGCGACCCG AGAAGGAGAA GGAGAACGCA  
 23101 CCGCATACCA CGCGCCACTG GGTGCTTTC ATTACGCCG CGCACTGTGC  
 GGCATATGGT GCGCGGTGAC CCAGCAGAAG TAAGTCGGCG GCGTGACACG  
 23151 GCTTACCTCC TTTGCCATGC TTGATTAGCA CCGGTGGGTT GCTGAAACCC  
 CGAATGGAGG AAACGGTACG AACTAATCGT GGCCACCCAA GCAGTTTGGG  
 23201 ACCATTGTGA GCGCCACATC TTCTTTTCT TCCTCGCTGT CCACGATTAC  
 TGGTAAACAT CCGGTGTAG AAGAGAAAAG AGGAGCGACA GGTGCTAATG  
 23251 CTCTGGTGAT GCGGGCGCTG CGGGCTTGGG AGAAGGGCGC TCTTTTTTCT  
 GAGACCACTA CCGCCCGCGA GCCCGAACCC TCTTCCCGCG AAGAAAAAGA  
 23301 TCTTGGGCGC AATGGCCAAA TCCGCCGCGG AGGTGCGATGG CCGCGGGCTG  
 AGAACC CGCG TTACCGTTT AGGCGGCGGC TCCAGCTACC GCGCGCCGAC  
 23351 GGTGTGCGCG GCACACGCGC GTCTTGTGAT GAGTCTTCCT CGTCTCGGA  
 CCACACGCGC CGTGTGCGC CAGAACACTA CTCAGAAGGA GCAGGAGCCT  
 23401 CTCGATACGC CGCCTCATCC GCTTTTTTGG GGGCGCCCGG GGAGGCGGCG  
 GAGCTATGCG GCGGAGTAGG CGAAAAAACC CCGCGGGGCC CCTCCGCGCG  
 23451 GCGACGGGGA CGGGGACGAC ACGTCTCTCA TGGTTGGGGG ACGTCGCGCC  
 CGCTGCCCTT GCCCTGCTG TGCAAGAGGT ACCAACCCCG TCAGCGCGCG  
 23501 GCACCGCGTC CGCGCTCGGG GGTGGTTTCG CGCTGCTCCT CTTCCGACT  
 CTGCGCGCAG GCGCGAGCCC CCACCAAAGC GCGACGAGGA GAAGGGCTGA  
 23551 GGCCATTTC TTTCTCTATA GGCAGAAAAA GATCATGGAG TCAGTCGAGA  
 CCGGTAAAGG AAGAGGATAT CCGTCTTTTT CTAGTACCTC AGTCAGCTCT  
 23601 AGAAGGACAG CCTAACCGCC CCTCTGAGT TCGCCACCAC CGCCTCCACC  
 TCTTCTGTG GGATTGGCGG GGGAGACTCA AGCGGTGGTG GCGGAGGTGG  
 23651 GATGCCGCCA ACGCGCTAC CACCTTCCCC GTCGAGGCAC CCCCCTTGA  
 CTACGGCGGT TGCGCGGATG GTGGAAGGGG CAGCTCCGTG GGGGCGAACT  
 23701 GGAGGAGGAA GTGATTATCG AGCAGGACCC AGGTTTTGTA AGCGAAGACG  
 CCTCTCCTT CACTAATAGC TCGTCTGGG TCCAAAACAT TCGCTTCTGC

FIG.9A-28

37/70

23751 ACGAGGACCG CTCAGTACCA ACAGAGGATA AAAAGCAAGA CCAGGACAAC  
 TGCTCCTGGC GAGTCATGGT TGTCTCCTAT TTTTCGTTCT GGTCTGTTTG  
 23801 GCAGAGGCAA ACGAGGAACA AGTCGGGCGG GGGGACGAAA GGCATGGCGA  
 CGTCTCCGTT TGCTCCTTGT TCAGCCCGCC CCCCTGCTTT CCGTACCGCT  
 23851 CTACCTAGAT GTGGGAGACG ACGTGTCTGT GAAGCATCTG CAGCGCCAGT  
 GATGGATCTA CACCTCTGCG TGCACGACAA CTTCTAGAC GTCGCGGTCA  
 23901 GCGCCATTAT CTGCGACGCG TTGCAAGAGC GCAGCGATGT GCCCTCGCC  
 CGCGGTAATA GACGCTGCGC AACGTCTCGG CGTCGCTACA CGGGAGCGGG  
 23951 ATAGCGGATG TCAGCCTTGC CTACGAAACG CACCTATTCT CACCGCGCT  
 TATCGCTAC AGTCGGAACG GATGCTTGCG GTGGATAAGA GTGGCGCGCA  
 24001 ACCCCCCAAA CGCCAAGAAA ACGGCACATG CGAGCCCAAC CGCGCCTCA  
 TGGGGGGTTT GCGGTTCTTT TGCCGTGTAC GCTCGGGTTG GGGCGGAGT  
 24051 ACTTCTACCC CGTATTTGCC GTGCCAGAGG TGCTTGCCAC CTATCACATC  
 TGAAGATGGG GCATAAACGG CACGGTCTCC ACGAACGGTG GATAGTGTAG  
 24101 TTTTTCAAA ACTGCAAGAT ACCCTATCC TGCCGTGCCA ACCGACGCC  
 AAAAAGGTTT TGACGTTCTA TGGGGATAGG ACGGCACGGT TGGCGTCGGC  
 24151 AGCGGACAAG CAGCTGGCCT TGCGGCAGGG CGCTGTCTA CCTGATATCG  
 TCGCCTGTTT GTCGACCGGA ACGCGTCCC GCGACAGTAT GGACTATAGC  
 24201 CCTCGCTCAA CGAAGTGCCA AAAATCTTTG AGGGTCTTGG ACGGCAGGAG  
 GGAGCGAGTT GCTTCACGGT TTTTAGAAAC TCCGAGAACC TCGCTGCTC  
 24251 AAGCGCGCGG CAAACGCTCT GCAACAGGAA AACAGCGAAA ATGAAAGTCA  
 TTCGCGCGCC GTTTGCGAGA CGTTGTCTT TTGTCGCTT TACTTTCACT  
 24301 CTCTGGAGTG TTGGTGGAAC TCGAGGGTGA CAACGCGCGC CTAGCCGTAC  
 GAGACCTCAC AACCACCTTG AGCTCCCACT GTTGCAGCGG GATCGGCATG  
 24351 TAAACGCGAG CATCGAGGTC ACCCAGTTTG CCTACCGGC ACTTAACCTA  
 ATTTTGCCTC GTAGCTCCAG TGGGTGAAAC GGATGGGCCG TGAATTGGAT  
 24401 CCCCCAAGG TCATGAGCAC AGTCATGAGT GAGCTGATCG TCGCCGTTGC  
 GGGGGGTTCC AGTACTCGTG TCAGTACTCA CTCGACTAGC ACGGCGACG  
 24451 GCAGCCCTTG GAGAGGGATG CAAATTTGCA AGAACAACA GAGGAGGGCC  
 CGTCGGGGAC CTCTCCCTAC GTTTAAACGT TCTTGTITGT CTCTCCCGG  
 24501 TACCCGAGT TGCGGACGAG CAGCTAGCGC GCTGGCTTCA AACGCGCGAG  
 ATGGGCGTCA ACCGCTGCTC GTCGATCGCG CGACCGAAGT TTGCGCGCTC  
 24551 CCTGCCGACT TGGAGGAGCG ACGCAACTA ATGATGGCG CAGTGTCTGT  
 GGACGGCTGA ACCTCTCGC TGCCTTTGAT TACTACCGGC GTCACGAGCA

FIG.9A-29

38/70

24601 TACCGTGGAG CTTGAGTGCA TGCAGCGGTT CTTTGCTGAC CCGGAGATGC  
 ATGGCACCTC GAACTCACGT ACGTCGCCAA GAAACGACTG GGCCTCTACG  
 24651 AGCGCAAGCT AGAGGAAACA TTGCACTACA CCTTTCGACA GGGCTACGTA  
 TCGCGTTCGA TCTCCTTTGT AACGTGATGT GAAAGCTGT CCCGATGCAT  
 24701 CGCGAGGCCT GCAAGATCTC CAACGTGGAG CTCTGCAACC TGGTCTCCTA  
 CGGCTCCGGA CGTTCTAGAG GTTGACCTC GAGACGTTGG ACCAGAGGAT  
 24751 CCTTGGAATT TTGCACGAAA ACCGCTTGG GCAAAACGTG CTTCAITCCA  
 GGAACCTTAA AACGTGCTTT TGGCGGAACC CGTTTTGCAC GAAGTAAAGT  
 24801 CGCTCAAGGG CGAGGCGCGC CGCGACTACG TCCGCGACTG CGTTTACTTA  
 GCGAGTTCCC GCTCCGCGCG GCGCTGATGC AGGCGCTGAC GCAATGAAT  
 24851 TTTCTATGCT ACACCTGGCA GACGGCCATG GCGGTTTGGC AGCAGTGCTT  
 AAAGATACGA TGTGGACCGT CTGCCGGTAC CCGCAACCG TCCTCAGCAA  
 24901 GGAGGAGTGC AACCTCAAGG AGCTGCAGAA ACTGCTAAAG CAAAACCTGA  
 CCTCTCACG TTGGAGTTCC TCGACGTCTT TGACGATTTT GTTTTGAAC  
 24951 AGGACCTATG GACGGCTTC AACGAGCGCT CCGTGGCCCG GCACCTGGCG  
 TCCTGGATAC CTGCCGGAAG TTGCTCGCGA GGCACCGCGC CGTGGACCGC  
 25001 GACATCATTT TCCCGAAGC CCTGCTTAAA ACCCTGCAAC AGGCTCTGCC  
 CTGTAGTAAA AGGGGCTTGC GGACGAATTT TGGGACGTTG TCCAGACGGG  
 25051 AGACTTCACC AGTCAAAGCA TGTTGCAGAA CTTTAGGAAC TTTATCCTAG  
 TCTGAAGTGG TCAGTTTCGT ACAACGTCTT GAAATCCTTG AAATAGGATC  
 25101 AGCGCTCAGG AATCTTGCCC GCCACCTGCT GTGCACTTCC TAGCGACTTT  
 TCGCGAGTCC TTAGAACGGG CGGTGGACGA CACGTGAAGG ATCGCTGAAA  
 25151 GTGCCCATTA AGTACCGCGA ATGCCCTCCG CCGCTTTGGG GCCACTTGTA  
 CACGGGTAAT TCATGGCGCT TACGGGAGGC GGCAGAACCC CGGTGACGAT  
 25201 CCTTCTGACG CTAGCCAAC ACCTTGCCCTA CCACTGTGAC ATAATGGAAG  
 GGAAGACGTC GATCGTTTGA TGGAACGGAT GGTGAGACTG TATTACCTTC  
 25251 ACGTGAGCGG TGACGGTCTA CTGGAGTGTG ACTGTGCTG CAACCTATGC  
 TGCACTCGCC ACTGCCAGAT GACCTACAG TGACAGCGAC GTTGGATACG  
 25301 ACCCGCACC GCTCCCTGGT TTGCAATTCG CAGCTGCTTA ACGAAAGTCA  
 TGGGGCGTGG CGAGGGACCA AACGTTAAGC GTCGACGAAT TGCTTTCAGT  
 25351 AATTATCGGT ACCTTTGAGC TGCAGGGTCC CTCGCCGTGAC GAAAAGTCCG  
 TTAATAGCCA TGGAACTCG ACGTCCAGG GAGCGGACTG CTTTTCAGGC  
 25401 CGGCTCCGGG GTTGAAACTC ACTCGGGGCG TGTGGACGTC GGCTTACCTT  
 GCGGAGGCC CAACCTTTGAG TGAGGCCCGG ACACCTGACG CCGAATGGAA

FIG.9A-30

39/70

25451 CGCAAAATTG TACCTGAGGA CTACCACGCC CACGAGATTA GGTCTACGA  
 GC GTTTAAAC ATGGACTCCT GATGGTCGCG GTGCTCTAAT CCAAGATGCT

25501 AGACCAATCC CGCCCGCCTA ATGCGGAGCT TACCGCCTGC GTCATTACCC  
 TCTGTTAGG GCGGGCGGAT TAGCCTCGA ATGGCGGACG CAGTAATGGG

25551 AGGGCCACAT TCTTGGCCAA TTGCAAGCCA TCAACAAAGC CCGCAAGAG  
 TCCCGTGTA AGAACC GGTT AACGTTGCGT AGTTGTTTCG GCGGTTCTCT

25601 TTTCTGCTAC GAAAGGACG GGGGGTTTAC TTGGACCCCC AGTCCGCGCA  
 AAAGACGATG CTTTCCCTGC CCCCAAATG AACCTGGGGG TCAGGCCGCT

25651 GGAGCTCAAC CCAATCCCC CGCCGCCGCA GCCCTATCAG CAGCAGCCGC  
 CCTCGAGTTG GGTAGGGGG GCGCGCGCGT CGGGATAGTC GTCGTCGGCG

25701 GGGCCCTTGC TTCCAGGAT GGCACCCAAA AAGAAGCTGC AGCTGCCGCC  
 CCCGGGAACG AAGGTCCTA CCGTGGGTTT TTCTTCGACG TCGACGCGCG

25751 GCCACCCACG GACGAGGAGG AATACTGGGA CAGTCAGGCA GAGGAGGTTT  
 CGGTGGGTGC CTGCTCCTCC TTATGACCCT GTGAGTCCGT CTCCTCCAAA

25801 TGGACGAGGA GGAGGAGGAC ATGATGGAAG ACTGGGAGAG CCTAGACGAG  
 ACCTGCTCCT CTTCTCCTG TACTACCTTC TGACCCTCTC GGATCTGCTC

25851 GAAGCTTCG AGGTCAAGA GGTGTGAGC GAAACACCGT CACCTCGGT  
 CTTCAAGGC TCCAGCTTCT CCACAGTCTG CTTTGTGGCA GTGGGAGCCA

25901 CGCATTCCCC TCGCCGGCGC CCCAGAAATC GGCAACCGGT TCCAGCATGG  
 GCGTAAGGGG AGCGGCCGCG GGGTCTTTAG CCGTTGGCCA AGTCTGATCC

25951 CTACAACCTC CGCTCCTCAG GCGCCGCGCG CACTGCCCGT TCGCCGACCC  
 GATGTTGGAG GCGAGGAGTC GCGGCCGCGC GTGACGGGCA AGCGCTGGG

26001 AACGCTAGAT GGGACACCAC TGGAACCAAG GCCGTAAGT CCAAGCAGCC  
 TTGGCATCTA CCTGTGGTG ACCTTGGTCC CGGCATTCA GGTTCTGTCG

26051 GCGCCCGTTA GCCCAAGAGC AACAACAGCG CCAAGGCTAC CGCTCATGGC  
 CGGCGGCAAT CGGGTTCTCG TTGTTGTGCG GGTTCGATG GCGAGTACCG

26101 GCGGGCACAA GAACGCCATA GTTGCTTGCT TGCAAGACTG TGGGGCAAC  
 CGCCCGTGT CTTGCGGTAT CAACGAACGA AGTTCGTGAC ACCCCGTTG

26151 ATCTCCTTCG CCCGCCGCTT TCTTCTCTAC CATCACGGCG TGGCTTCCC  
 TAGAGGAAGC GGGCGGCGAA AGAAGAGATG GTAGTGCCCG ACCGGAAGGG

26201 CGGTAAATC CTGCATTACT ACCGTCTATC CTACAGCCCA TACTGCACCG  
 GGATTGTAG GACGTAATGA TGGCAGTAGA GATGTCGGGT ATGACGTGGC

26251 GCGGCAGCGG CAGCAACAGC AGCGGCCACA CAGAAGCAA GCGACCGGA  
 CGCCGTGCG GTGCTGTGCG TCGCCGGTGT GTCTTCGTTT CCGCTGGCCT

FIG. 9A-31

40/70

26301 TAGCAAGACT CTGACAAAGC CCAAGAAATC CACAGCGGCG GCAGCAGCAG  
 ATCGTTCTGA GACTGTTTCG GGTCTTTAG GTGTCGCCGC GTGCTGCTGC  
 26351 GAGGAGGAGC GCTGCGTCTG GCGCCCAACG AACCCGTATC GACCCGCGAG  
 CTCCTCCTCG CGACGCAGAC CCGGGGTTGC TTGGGCATAG CTGGGCGCTC  
 26401 CTTAGAAACA GGATTTTTCC CACTCTGTAT GCTATATTTC AACAGAGCAG  
 GAATCTTTGT CCTAAAAAGG GTGAGACATA CGATATAAAG TTGCTCGTGC  
 26451 GGGCCAAGAA CAAGAGCTGA AAATAAAAAA CAGGTCTCTG CGATCCCTCA  
 CCCGGTTCCT GTTCTCGACT TTTATTTTTT GTCCAGAGAC GCTAGGGAGT  
 26501 CCCGCAGCTG CCTGTATCAC AAAAGCGAAG ATCAGCTTCG GCGCACGCTG  
 GGGCGTCGAC GGACATAGTG TTTTCGTTTC TAGTCGAAGC GCGGTGCGAC  
 26551 GAAGACGCGG AGGCTCTCTT CAGTAAATAC TGC GCGCTGA CTCTTAAGGA  
 CTTCTGCGCC TCCGAGAGAA GTCAATTTATG ACGCGCGACT GAGAATTCCT  
 26601 CTAGTTCGCG GCCCTTTCTC AAATTTAAGC GCGAAACTA CGTCATCTCC  
 GATCAAAGCG CGGGAAGAGG TTAAATTCG CGCTTTTGAT GCGATGAGAG  
 26651 AGCGGCCACA CCCGCGCCA GCACCTGTTG TCAGGCGCAT TATGAGCAAG  
 TCGCGGTGT GGGCGCGGT CGTGGAACAAC AGTCGCGGTA ATACTCGTTC  
 26701 GAAATCCCA CGCCCTACAT GTGGAGTTAC CAGCCACAAA TGGGACTTGC  
 CTTTAAGGGT GCGGGATGTA CACCTCAATG GTGCGGTGTT ACCCTGAACG  
 26751 GGCTGGAGCT GCCCAAGACT ACTCAACCCG AATAAACTAC ATGAGCGCGG  
 CCGACTCGA CGGGTTCTGA TGAGTTGGGC TTATTTGATG TACTCGCGCC  
 26801 GACCCACAT GATATCCCG GTCAACGGAA TACGCGCCCA CCGAAACCGA  
 CTGGGGTGTA CTATAGGGCC CAGTTGCCCT ATGCGCGGGT GGCCTTGCT  
 26851 ATTCTCTGG AACAGCGGCG TATTACCACC ACACCTCGTA ATAACCTTAA  
 TAAGAGGACC TTGTCCGCGG ATAATGGTGG TGTGGAGCAT TATTGGAATT  
 26901 TCCCCGTAGT TGGCCCGCTG CCCTGGTGTA CCAGGAAAGT CCCGCTCCCA  
 AGGGGCATCA ACCGGGCGAC GGGACCACAT GGTCTTTCA GGGCGAGGGT  
 26951 CCACTGTGGT ACTTCCAGA GACGCCAGG CCGAAGTTCA GATGACTAAC  
 GGTGACACCA TGAAGGGTCT CTGCGGGTCC GGCTTCAAGT CTACTGATTG  
 27001 TCAGGGGCGC AGCTTGCGGG GCGCTTTCTG CACAGGGTGC GGTGCGCCGG  
 AGTCCCCGCG TCGAACGCC GCGGAAAGCA GTGTCCACG CAGCGGGCC  
 27051 GCAGGGTATA ACTCACCTGA CAATCAGAGG GCGAGGTATT CAGCTCAACG  
 CGTCCCATAT TGAGTGGACT GTTAGTCTCC CGCTCCATAA GTCGAGTTGC  
 27101 ACGAGTCGGT GAGCTCCTCG CTGGTCTCC GTCCGGACGG GACATTTGAG  
 TGCTCAGCCA CTCGAGGAGC GAACCAAGAG CAGGCTGCC CTGTAAAGTC

FIG.9A-32

## 41/70

27151 ATCGGGCGCG CGGGCGCTC TTCATTCACG CCTCGTCAGG CAATCCTAAC  
 TAGCCGCCGC GGCCGGCGAG AAGTAAGTGC GGAGCAGTCC GTTAGGATTG  
 27201 TCTGCAGACC TCGTCTCTG AGCGCGCTC TGGAGGCATT GGAACCTGCG  
 AGACGTCTGG AGCAGGAGAC TCGGCGCGAG ACCTCCGTAA CCTTGAGACG  
 27251 AATTTATTGA GGAGTTTGTG CCATCGGTCT ACTTTAACCC CTCTCGGGGA  
 TTAAATAACT CCTCAACAC GGTAGCCAGA TGAATTGGG GAAGAGCCCT  
 27301 CCTCCCGGCC ACTATCCGGA TCAATTTATT CCTAACTTTG ACGCGGTAA  
 GGAGGGCCGG TGATAGGCCT AGTTAAATAA GGATTGAAAC TGCGCCATT  
 27351 GGACTCGGCG GACGGCTACG ACTGAATGTT AAGTGGAGAG GCAGAGCAAC  
 CCTGAGCCGC CTGCCGATGC TGACTTACAA TTCACCTCTC CGTCTCGTTG  
 27401 TGCGCCGAA ACACCTGGTC CACTGTCGCC GCCACAAGTG CTTTGCCCGC  
 ACGCGGACTT TGTGGACCAG GTGACAGCG CGGTGTTTAC GAAACGGGCG  
 27451 GACTCCGGTG AGTTTTGCTA CTTTGAATTG CCCGAGGATC ATATCGAGGG  
 CTGAGGCCAC TCAAAACGAT GAAACTTAAC GGGCTCCTAG TATAGTCCC  
 27501 CCCGGCGCAC GGCCTCCGGC TTACCGCCCA GGGAGAGCTT GCCCGTAGCC  
 GGGCCGCGTG CCGCAGGCCG AATGGCGGGT CCCTCTCGAA CGGGCATCGG  
 27551 TGATTCGGGA GTTTACCCAG CGCCCCCTGC TAGTTGAGCG GGACAGGGGA  
 ACTAAGCCCT CAAATGGGCT GGGGGGACG ATCAACTCGC CCTGTCCCCT  
 27601 CCCTGTGTTT TCACTGTGAT TTGCAACTGT CCTAACCTTG GATTACATCA  
 GGGACACAAG AGTGACACTA AACGTTGACA GGATTGGGAC CTAATGTAGT  
 27651 AGATCTTTGT TGCCATCTCT GTGCTGAGTA TAATAAATAC AGAAATTAAT  
 TCTAGAAAA ACGGTAGAGA CACGACTCAT ATTATTTATG TCTTTAATTT  
 27701 ATATACTGGG GCTCCTATCG CCATCTGTGA AACGCCACCG TCTTACCCCG  
 TATATGACCC CGAGGATAGC GGTAGACAT TTGCGGTGGC AGAAGTGGG  
 27751 CCCAAGCAAA CCAAGGCGAA CCTTACCTGG TACTTTTAAC ATCTCTCCCT  
 GGGTTCTGTT GGTTCCGCTT GGAATGGACC ATGAAAATTG TAGAGAGGGA  
 27801 CTGTGATTTA CAACAGTTTC AACCCAGACG GAGTGAGTCT ACGAGAGAAC  
 GACACTAAAT GTTGTCAAAG TTGGGTCTGC CTCACTCAGA TGCTCTCTTG  
 27851 CTCTCCGAGC TCAGCTACTC CATCAGAAAA AACACCACC TCCTTACCTG  
 GAGAGGCTCG AGTCGATGAG GTAGTCTTTT TTGTGGTGGG AGGAATGGAC  
 27901 CCGGGAACGT ACGAGTGCCT CACCGGCCCG TGCACCACAC CTACCGCCTG  
 GGCCCTTGCA TGCTACGCA GTGGCCGGCG ACGTGGTGTG GATGGCGGAC  
 27951 ACCGTAAACG AGACTTTTTT CGGACAGACC TCAATAACTC TGTTTACCAG  
 TGGCATTTGG TCTGAAAAG GCCTGTCTGG AGTTATTGAG ACAATGGTC

FIG.9A-33

42/70

28001 AACAGGAGGT GAGCTTAGAA ACCCTTAGG GTATTAGGCC AAGGCGCAG  
 TTGCTCTCCA CTCGAATCTT TTGGGAATCC CATAATCCGG TTTCGCCGTC

28051 CTA CTGTGGG GTTTATGAAC AATTCAAGCA ACTCTACGGG CTATTCTAAT  
 GATGACACCC CAAATACCTG TTAAGTTCGT TGAGATGCC GATAAGATTA

28101 TCAGGTTTCT CTAGAATCGG GGTGGGGTT ATTCTCTGTC TTGTGATTCT  
 AGTCCAAAGA GATCTTAGCC CCAACCCCAA TAAGAGACAG AACACTAAGA

28151 CTTTATTCTT ATACTAACGC TTCTCTGCCT AAGGCTCGCC GCCTGCTGTG  
 GAAATAAGAA TATGATTGCG AAGAGACGGA TTCCGAGCGG CGGACGACAC

28201 TGCACATTGG CATTTATTGT CAGCTTTTTA AACGCTGGGG TCGCCACCCA  
 ACGTGTAAAC GTAAATAACA GTCGAAAAAT TTGCGACCCC AGCGGTGGGT

28251 AGATGATTAG GTACATAATC CTAGGTTTAC TCACCCCTGC GTCAGCCAC  
 TCTACTAATC CATGTATTAG GATCCAAATG AGTGGGAACG CAGTCGGGTG

28301 GGTACCACCC AAAAGGTGGA TTTTAAGGAG CCAGCCTGTA ATGTTACATT  
 CCATGGTGGG TTTTCCACCT AAAATTCTCT GGTGCGACAT TACAATGTAA

28351 CGCAGCTGAA GCTAATGAGT GCACCACTCT TATAAAATGC ACCACAGAAC  
 GCGTCGACTT CGATTACTCA CGTGGTGAGA ATATTTTACG TGGTGTCTTG

28401 ATGAAAAGCT GCTTATTCGC CACAAAAACA AAATTGGCAA GTATGCTGTT  
 TACTTTTCGA CGAATAAGCG GTGTTTTGT TTTAACCCTT CACACGACAA

28451 TATGCTATTT GGCAGCCAGG TGACACTACA GAGTATAATG TTACAGTTTT  
 ATACGATAAA CCGTCGGTCC ACTGTGATGT CTCATATTAC AATGTCAAAA

28501 CCAGGGTAAA AGTCATAAAA CTTTATGTA TACTTTTCCA TTTTATGAAA  
 GGTCCCATTT TCAGTATTTT GAAAATACAT ATGAAAAGGT AAAATACTTT

28551 TGTGCGACAT TACCATGTAC ATGAGCAAAC AGTATAAGTT GTGGCCCCCA  
 ACACGCTGTA ATGGTACATG TACTCGTTTG TCATATTTCA CACCGGGGGT

28601 CAAAATTGTG TGGAAACAC TGGCACTTTC TGCTGCACTG CTATGCTAAT  
 GTTTTAAACAC ACCTTTGTG ACCGTGAAG ACGACGTGAC GATACGATTA

28651 TACAGTGCTC GCTTTGGTCT GTACCCTACT CTATATTAAA TACAAAAGCA  
 ATGTCACGAG CGAAACCAGA CATGGGATGA GATATAATTT ATGTTTTCGT

28701 GACGCAGCTT TATTGAGGAA AAGAAAATGC CTTAATTTAC TAAGTTACAA  
 CTGCGTCGAA ATAACTCCTT TTCCTTTACG GAATTAATG ATTCATGTT

28751 AGCTAATGTC ACCACTAACT GCTTACTCGT CTGCTTGCAA AACAAATCA  
 TCGATTACAG TGGTGATTGA CGAAATGAGC GACGAACGTT TTGTTTAAGT

28801 AAAAGTTAGC ATTATAATTA GAATAGGATT TAAACCCCCC GGTCAATTTCC  
 TTTTCAATCG TAATATTAAT CTTATCCTAA ATTTGGGGGG CAGTAAAGG

FIG.9A-34

43/70

28851 TGCTCAATAC CATTCCCTG AACAATTGAC TCTATGTGGG ATATGCTCCA  
 ACGAGTTATG GTAAGGGGAC TTGTTAACTG AGATACACCC TATACGAGGT  
 28901 GCGCTACAAC CTTGAAGTCA GGCTTCTGG ATGTGAGCAT CTGACTTTGG  
 CGGATGTTG GAACCTCAGT CCGAAGGACC TACAGTCGTA GACTGAAACC  
 28951 CCAGCACCTG TCCCGCGGAT TTGTTCCAGT CCAACTACAG CGACCCACCC  
 GGTCTGTGGAC AGGGCGCCTA ACAAAGGTCA GGTTGATGTC GCTGGGTGGG  
 29001 TAACAGAGAT GACCAACACA ACCAACGCGG CCGCCGTAC CGGACTTACA  
 ATGTCTCTA CTGGTTGTGT TGTTGCGCC GCGGCGCATG GCCTGAATGT  
 29051 TCTACCACAA ATACACCCCA AGTTCGTGC TTTGTCAATA ACTGGGATAA  
 AGATGGTGTT TATGTGGGT TCAAAGACGG AAACAGTTAT TGACCTATT  
 29101 CTTGGGCATG TGGTGGTTCT CCATAGCGCT TATGTTTGT TGCCTTATTA  
 GAACCCGTAC ACCACCAAGA GGTATCGCGA ATACAACAT ACGGAATAAT  
 29151 TTATGTGGCT CATCTGCTGC CTAAAGCGCA AACGCGCCG ACCACCCATC  
 AATACACCGA GTAGACGACG GATTTCGCGT TTGCGCGGGC TGGTGGGTAG  
 29201 TATAGTCCCA TCATTGTGCT ACACCCAAC AATGATGGAA TCCATAGATT  
 ATATCAGGGT AGTAACCGA TGTGGGTTTG TTACTACCT AGGTATCTAA  
 29251 GGACGGACTG AAACACATGT TCCTTTCTCT TACAGTATGA TTAATGAGA  
 CCTGCCTGAC TTTGTGTACA AGAAAAAGAGA ATGTCATACT AATTTACTCT  
 29301 CATGATTCTT CGAGTTTTTA TATTACTGAC CCTGTTGCG CTTTTTGTG  
 GTACTAAGGA GCTCAAAAT ATAATGACTG GGAACAACGC GAAAAAACAC  
 29351 CGTGCTCCAC ATTGGCTGCG GTTTCACACA TCGAAGTAGA CTGCATTCCA  
 GCACGAGGTG TAACCGACGC CAAAGAGTGT AGCTTCATCT GACGTAAGGT  
 29401 GCCTTCACAG TCTATTTGCT TTACGGATT GTCAACCCTA CGCTCATCTG  
 CGGAAGTGTC AGATAACGA AATGCCATAA CAGTGGGAGT GCGAGTAGAC  
 29451 CAGCCTCATC ACTGTGGTCA TCGCCTTAT CAGTGCATT GACTGGGTCT  
 TCGGAGTAGT TGACACCATG AGCGGAAATA GGTACAGTAA CTGACCAGA  
 29501 GTGTGCGCTT TGCATATCTC AGACACCATC CCCAGTACAG GGACAGGACT  
 CACACGCGAA ACGTATAGAG TCTGTGGTAG GGGTCATGTC CCTGCTCTGA  
 29551 ATAGCTGAGC TTCTTAGAAT TCTTTAATTA TGAATTTAC TGTGACTTTT  
 TATCGACTCG AAGAATCTTA AGAAATTAAT ACTTTAAATG ACAGTAAAAA  
 29601 CTGCTGATTA TTTGCACCT ATCTGCGTTT TGTTCCCGGA CCTCCAAGCC  
 GACGACTAAT AAACGTGGGA TAGACGCAAA ACAAGGGGCT GGAGGTTTCGG  
 29651 TCAAAGACAT ATATCATGCA GATTCACTCG TATATGGAAT ATTCCAAGTT  
 AGTTTCTGTA TATAGTACGT CTAAGTGAGC ATATACCTTA TAAGGTTCAA

FIG.9A-35

## 44/70

29701 GCTACAATGA AAAAAGCGAT CTTTCGGAAG CCTGGTTATA TGCAATCATC  
 CGATGTTACT TTTTTCGCTA GAAAGGCTTC GGACCAATAT ACGTTAGTAG  
 29751 TCTGTTATGG TGTTCGTCAG TACCATCTTA GCCCTAGCTA TATATCCCTA  
 AGACAATACC ACAAGACGTC ATGGTAGAAT CGGGATCGAT ATATAGGGAT  
 29801 CCTTGACATT GGCTGGAACG CAATAGATGC CATGAACCA CCAACTTTCC  
 GGAACGTAA CCGACCTTGC GTTATCTACG GTACTTGGTG GGTGAAAGG  
 29851 CCGCGCCCGC TATGCTTCCA CTGCAACAAG TTGTTGCCGG CGGCTTTGTC  
 GGC CGCGGCG ATACGAAGT GACGTTGTTC AACACGCGCC GCCGAAACAG  
 29901 CCAGCCAATC AGCCTCGCCC ACCTTCTCCC ACCCCCACTG AAATCAGCTA  
 GGTGCGTTAG TCGAGCGGG TGAAGAGGG TGGGGGTGAC TTTAGTCGAT  
 29951 CTTTAATCTA ACAGGAGGAG ATGACTGACA CCCTAGATCT AGAAATGGAC  
 GAAATTAGAT TGTCTCCTC TACTGACTGT GGGATCTAGA TCTTTACCTG  
 30001 GGAATTATTA CAGAGCAGCG CCTGCTAGAA AGACGCAGGG CAGCGGCCGA  
 CCTTAATAAT GTCTCGTCGC GGACGATCTT TCTGCGTCCC GTCGCCGGCT  
 30051 GCAACAGCGC ATGAATCAAG AGCTCCAAGA CATGGTTAAC TTGACCCAGT  
 CGTTGTCGCG TACTTAGTTC TCGAGGTTCT GTACCAATTG ACGTGGTCA  
 30101 GCAAAAGGGG TATCTTTTGT CTGCTAAAGC AGGCCAAAGT CACCTACGAC  
 CGTTTTCCCC ATAGAAAACA GAGCATTTCC TCCGGTTTCA GTGGATGCTG  
 30151 AGTAATACCA CCGGACACCG CCTTAGCTAC AAGTTGCCAA CCAAGCGTCA  
 TCATTATGGT GGCCTGTGGC GGAATCGATG TTCAACGGTT GTTTCGCACT  
 30201 GAAATTGGTG GTCATGGTGG GAGAAAAGCC CATTACCATA ACTCAGCACT  
 CTTAACCAC CAGTACCACC CTCTTTTCGG GTAATGGTAT TGAGTCGTGA  
 30251 CGGTAGAAAC CGAAGGCTGC ATTCACCTCAC CTTGTCAAGG ACCTGAGGAT  
 GCCATCTTTG GCTTCCGACG TAAGTGAGTG GAACAGTTCC TAGACTCCTA  
 30301 CTCTGCACCC TTATTAAGAC CCTGTGCGGT CTCAAAGATC TTATTCCCTT  
 GAGACGTGGG AATAATTCTG GGACACGCCA GAGTTTCTAG AATAAGGGAA  
 30351 TAACTAATAA AAAAAAATAA TAAAGCATCA CTTACTTAAA ATCAGTTAGC  
 ATTGATTATT TTTTTTTATT ATTTCTGAGT GAATGAATTT TAGTCAATCG  
 30401 AAATTTCTGT CCAGTTTATT CAGCAGCACC TCCTTGCCCT CCTCCAGCT  
 TTTAAAGACA GTGCAAAATA GTGCTGCTGG AGGAACGGGA GGAGGGTCA  
 30451 CTGGTATTGC AGCTTCTCC TGGCTGCAAA CTTTCTCCAC AATCTAAATG  
 GACCATAACG TCGAAGGAGG ACCGACGTTT GAAAGAGGTG TTAGATTTCAT  
 30501 GAATGTCAGT TTCTCCTGT TCCTGTCCAT CCGCACCCAC TATCTTCATG  
 CTTACAGTCA AAGGAGGACA AGGACAGGTA GCGTGGGTG ATAGAAGTAC

FIG.9A-36

45/70

30551 TTGTTGCAGA TGAAGCGCGC AAGACCGTCT GAAGATACCT TCAACCCCGT  
 AACACAGTCT ACTTCGCGCG TTCTGGCAGA CTTCATATGA AGTTGGGGCA  
 30601 GTATCCATAT GACACGGAAA CCGGTCTCTC AACTGTGCCT TTTCTTACTC  
 CATAGGTATA CTGTGCCCTT GGCACGGAGG TTGACACGGA AAAGAATGAG  
 30651 CTCCCTTTGT ATCCCCAAT GGGTTTCAAG AGAGTCCCCC TGGGGTACTC  
 GAGGGAAACA TAGGGGGTTA CCCAAAGTTC TCTCAGGGGG ACCCCATGAG  
 30701 TCTTTGCGCC TATCCGAACC TCTAGTTACC TCCAATGGCA TGCTTGCCT  
 AGAAACGCGG ATAGGCTTGG AGATCAATGG AGGTTACCGT ACGAACGCGA  
 30751 CAAAATGGGC AACGGCCTCT CTCTGGACGA GGC CGGCAAC CTTACCTCCC  
 GTTTTACCCG TTGCCGGAGA GAGACCTGCT CCGGCCGTTG GAATGGAGGG  
 30801 AAAATGTAAC CACTGTGAGC CCACCTCTCA AAAAAACCAA GTCAAACATA  
 TTTTACATTG GTGACACTCG GGTGGAGAGT TTTTTTGTT CAGTTTGAT  
 30851 AACCTGAAAA TATCTGCACC CCTCAGATT ACCTCAGAA G CCTAAGTGT  
 TTGACCTTT ATAGACGTGG GGAGTGTCAA TGGAGTCTTC GGGATTGACA  
 30901 GGTGCGCGCC GCACCTCTAA TGGTCCGGGG CAACACACTC ACCATGCAAT  
 CCGACGGCGG CGTGAGAGT ACCAGCGCCC GTTGTGTGAG TGGTACGTTA  
 30951 CACAGGCCCC GCTAACCGTG CACGACTCCA AACTTAGCAT TGCCACCAA  
 GTGTCCGGGG CGATTGGCAC GTGCTGAGGT TTGAATCGTA ACGTGGGTT  
 31001 GGACCCCTCA CAGTGTGAGA AGGAAAGCTA GCCCTGCAAA CATCAGGCC  
 CCTGGGGAGT GTCACAGTCT TCCTTTCGAT CGGGACGTTT GTAGTCCGGG  
 31051 CCTCACCACC ACGGATAGCA GTACCCCTTAC TACTACTGCC TCACCCCTT  
 GGAGTGTGG TGCTATCGT CATGGGAATG ATAGTGACGG AGTGGGGGAA  
 31101 TAACTACTGC CACTGGTAGC TTGGGCATTG ACTTGAAAGA GCCCATTAT  
 ATTGATGACG GTGACCATCG AACCCGTAAC TGAACCTTCT CCGGTAAATA  
 31151 ACACAAAATG GAAAACTAGG ACTAAAGTAC GGGGCTCCTT TGCATGAAC  
 TGTGTTTTAC CTTTTGATCC TGATTTTCATG CCCCAGGAA ACGTACATTG  
 31201 AGACGACCTA AACACTTTGA CCGTAGCAAC TGGTCCAGGT GTGACTATTA  
 TCTGCTGGAT TTGTGAACT GGCATCGTTG ACCAGGTCCA CACTGATAAT  
 31251 ATAATACTTC CTTGCAAACCT AAAGTTACTG GAGCCTTGGG TTTTGATTCA  
 TATTATGAAG GAACGTTTGA TTTCAATGAC CTCGGAACCC AAACTAAGT  
 31301 CAAGGCAATA TGCAACTTAA TGTAGCAGGA GGAATAAGGA TTGATTCTCA  
 GTCCGTTAT ACGTTGAATT ACATCGTCTT CCGATTCTT AACTAAGAGT  
 31351 AAACGACGCG CTTATACTTG ATGTTAGTTA TCCGTTTGT GCTCAAAACC  
 TTTGTCTGCG GAATATGAAC TACAATCAAT AGGCAAACTA CGAGTTTGG

FIG.9A-37

46/70

31401 AACTAAATCT AAGACTAGGA CAGGGCCCTC TTTTATAAA CTCAGCCCAC  
 TTGATTTAGA TTCTGATCCT GTCCCGGGAG AAAAATAITTT GAGTCGGGTG  
 31451 AACTTGGATA TTAACACAA CAAAGGCCTT TACTTGTTTA CAGCTTCAAA  
 TTGAACCTAT AATTGATGTT GTTCCGGAA ATGAACAAAT GTCGAAGTTT  
 31501 CAATTCCAAA AAGCTTGAGG TTAACCTAAG CACTGCCAAG GGGTTGATGT  
 GTTAAGGTTT TTCGAACCTC AATTGGATTC GTGACGGTTC CCCAACTACA  
 31551 TTGACGCTAC AGCCATAGCC ATTAATGCAG GAGATGGGCT TGAATTTGGT  
 AACTGCGATG TCGGTATCGG TAATTACGTC CTCTACCCGA ACTTAAACCA  
 31601 TCACCTAATG CACCAAAAC AAATCCCCTC AAAACAAAA TTGGCCATGG  
 AGTGGATTAC GTGGTTTGTG TTTAGGGGAG TTTTGTTTTT AACCGGTACC  
 31651 CCTAGAATTT GATTCAAACA AGGCTATGGT TCCTAAACTA GGAAGTGGCC  
 GGATCTTAAA CTAAGTTTGT TCCGATACCA AGGATTGAT CCTTGACCGG  
 31701 TTAGTTTTGA CAGCACAGGT GCCATTACAG TAGGAACAAA AAATAATGAT  
 AATCAAACT GTCGTGTCCA CGGTAAATGTC ATCCTTTGTT TTTATTACTA  
 31751 AAGCTAACTT TGTGGACCAC ACCAGCTCCA TCTCCTAACT GTAGACTAAA  
 TTCGATTGAA ACACCTGGTG TGGTCGAGGT AGAGGATTGA CATCTGAATTT  
 31801 TGCAGAGAAA GATGCTAAAC TCACTTTGGT CTTAACAAAA TGTGGCAGTC  
 ACGTCTCTTT CTACGATTTG AGTGAAACCA GAATTTGTTT ACACCGTCAG  
 31851 AAATACTTGC TACAGTTTCA GTTTTGGCTG TTAAGGCAG TTTGGCTCCA  
 TTTATGAACG ATGTCAAAGT CAAAACCGAC AATTTCCGTC AAACCGAGGT  
 31901 ATATCTGGAA CAGTTCAAAG TGCTCATCTT ATTATAAGAT TTGACGAAAA  
 TATAGACCTT GTCAAGTTTC ACGAGTAGAA TAATATTCTA AACTGCTTTT  
 31951 TGGAGTGCTA CTAACAATT CCTTCCTGGA CCCAGAATAT TGGAACTTTA  
 ACCTCACGAT GATTTGTAA GGAAGGACCT GGGTCTTATA ACCTGAAAT  
 32001 GAAATGGAGA TCTTACTGAA GGCACAGCCT ATACAAACGC TGTGTGATTT  
 CTTTACCTCT AGAATGACTT CCGTGTGCGA TATGTTTGGC ACAACCTAAA  
 32051 ATGCCTAACC TATCAGCTTA TCCAAAATCT CACGGTAAAA CTGCCAAAAG  
 TACGGAATTG ATAGTCGAAT AGGTTTTAGA GTGCCATTTT GACGGTTTTT  
 32101 TAACATTGTC AGTCAAGTTT ACTTAAACGG AGACAAAACCT AAACCTGTAA  
 ATTGTAACAG TCAGTTCAAA TGAATTTGCC TCTGTTTTGA TTTGGACATT  
 32151 CACTAACCAT TACACTAAAC GGTACACAGG AAACAGGAGA CACAACCTCA  
 GTGATTGGTA ATGTGATTG CCATGTGTCC TTTGTCCTCT GTGTGAGGT  
 32201 AGTGCATAC CTATGTCATT TTCATGGGAC TGGTCTGGCC ACAACTACAT  
 TCACGTATGA GATACAGTAA AAGTACCCGT ACCAGACCGG TGTTGATGTA

FIG.9A-38

## 47/70

32251 TAATGAAATA TTTGCCACAT CCTCTTACAC TTTTTCATAC ATTGCCCAAG  
 ATTACTTTAT AAACGGTGTA GGAGAATGTG AAAAAGTATG TAACGGGTTC  
 32301 AATAAAGAAT CGTTTGTGTT ATGTTTCAAC GTGTTTATTT TTCAATTGCA  
 TTATTTCTTA GCAACACAA TACAAAGTTG CACAAATAAA AAGTTAACGT  
 32351 GAAAAATTCA AGTCAITTTT CATTAGTAG TATAGCCCA CCACCACATA  
 CTTTTAAAGT TCAGTAAAA GTAAGTCATC ATATCGGGT GGTGGTGTAT  
 32401 GCTTATACAG ATCACCCTAC CTTAATCAAA CTCACAGAAC CCTAGTATTC  
 CGAATATGTC TAGTGGCATG GAATTAGTTT GAGTGTCTTG GGATCATAAG  
 32451 AACCTGCCAC CTCCTCCCA ACACACAGAG TACACAGTCC TTTCTCCCCG  
 TTGGACGGTG GAGGGAGGGT TGTGTCTC ATGTGTCAGG AAAGAGGGGC  
 32501 GCTGGCCTTA AAAAGCATCA TATCATGGGT AACAGACATA TTCTTAGGTG  
 CGACCGGAAT TTTTCGTAGT ATAGTACCCA TTGTCTGTAT AAGAAATCCAC  
 32551 TTATATTCCA CACGGTTTCC TGTGAGCCA AACGCTCATC AGTGATATTA  
 AATATAAGGT GTGCCAAAGG ACAGCTCGGT TTGCGAGTAG TCACATAAT  
 32601 ATAAACTCCC CGGGCAGCTC ACTTAAGTTC ATGTGCGTGT CCAGCTGCTG  
 TATTTGAGGG GCCGTCGAG TGAATTCAG TACAGCGACA GGTGACGAC  
 32651 AGCCACAGGC TGCTGTCCAA CTTGCGGTTG CTTAACGGGC GCGAAGGAG  
 TCGGTGTCCG ACGACAGGTT GAACGCCAAC GAATTGCCCG CCGCTTCTC  
 32701 AAGTCCACGC CTACATGGGG GTAGAGTCAT AATCGTGCAT CAGGATAGGG  
 TTCAGGTGCG GATGTACCCC CATCTCAGTA TTAGCACGTA GTCCTATCCC  
 32751 CGGTGGTGCT GCAGCAGCGC GCGAATAAAC TGCTGCCGCC GCCGCTCCGT  
 GCCACCACGA CGTCGTCGCG CGCTTATTTG ACGACGCGCG CGGCGAGGCA  
 32801 CCTGCAGGAA TACAACATGG CAGTGGTCTC CTCACGATG ATTCGCACCG  
 GGACGTCTTT ATGTTGTACC GTCACAGAG GAGTCGCTAC TAAGCGTGCG  
 32851 CCCGCAGCAT AAGCGCCTT GTCCTCCGG CACAGCAGCG CACCCTGATC  
 GGGCGTCGTA TTCCGCGGAA CAGGAGGCCG GTGTGTCGCG GTGGGACTAG  
 32901 TCACTTAAAT CAGCACAGTA ACTGCAGCAC AGCACCACAA TATTGTTCAA  
 AGTGAATTTA GTCGTGTCAT TGACGTCGTG TCGTGGTGTT ATAACAGTT  
 32951 AATCCCACAG TGCAAGGCGC TGTATCCAAA GCTCATGGCG GGGACCACAG  
 TTAGGGTGTC ACCTTCCGCG ACATAGGTTT CAGTACCCG CCTTGGTGTG  
 33001 AACCCACGTG GCCATCATAC CACAAGCGCA GGTAGATTA GTGGCGACCC  
 TTGGGTGCAC CGGTAGTAGT GTGTTGCGGT CCATCTAATT CACCGCTGGG  
 33051 CTCATAAACA CGCTGGACAT AAACATTACC TCTTTGGCA TGTGTAAAT  
 GAGTATTTGT GCGACCTGTA TTTGTAATGG AGAAAAACCGT ACAACATTAA

FIG.9A-39

48/70

33101 CACCACCTCC CGGTACCATA TAAACCTCTG ATTAACATG GCGCCATCCA  
 GTGGTGGAGG GCCATGGTAT ATTTGGAGAC TAATTTGTAC CCGCGTAGGT

33151 CCACCATCCT AAACCAGCTG GCCAAAACCT GCCCGCGGCG TATACACTGC  
 GGTGGTAGGA TTGGTCGAC CGGTTTTGGA CGGGCGGCCG ATATGTGACG

33201 AGGGAACCGG GACTGGAACA ATGACAGTGG AGAGCCGAGG ACTCGTAACC  
 TCCCTTGCC CTGACCTTGT TACTGTCACC TCTCGGTCC TGAGCATTGG

33251 ATGGATCATC ATGCTCGTCA TGATATCAAT GTTGGCACA CACAGGCACA  
 TACCTAGTAG TACGAGCAGT ACTATAGTTA CAACCGTGT GTGTCCGTGT

33301 CGTGCATACA CTTCCTCAGG ATTACAAGCT CCTCCGCGT TAGAACCAT  
 GCACGTATGT GAAGGAGTCC TAATGTTGCA GGAGGGCGCA ATCTTGGTAT

33351 TCCCAGGGAA CAACCCATTC CTGAATCAGC GTAAATCCCA CACTGCAGGG  
 AGGGTCCCTT GTTGGGTAGG GACTTAGTCG CATTTAGGGT GTGACGTCCC

33401 AAGACCTCGC ACGTAACTCA CGTTGTGCAT TGTCAAAGTG TTACATTCGG  
 TTCTGGAGCG TGCATTGAGT GCAACACGTA ACAGTTTCAC AATGTAAGCC

33451 GCAGCAGCGG ATGATCCTCC AGTAGTGTAG CGCGGGTTTC TGTCTCAAAA  
 CGTCGTCGCC TACTAGGAGG TCATACCATC GCGCCCAAAG ACAGAGTTTT

33501 GGAGGTAGAC GATCCCTACT GTACGGAGTG CGCCGAGACA ACCGAGATCG  
 CCTCCATCTG CTAGGGATGA CATGCCCTAC GCGGCTCTGT TGGCTCTAGC

33551 TGTGGTGGT AGTGTGATGC CAAATGGAAC GCCGGACGTA GTCATATTT  
 ACAACGAGCA TCACAGTAGG GTTTACCTTG CGGCTGTCAT CAGTATAAAG

33601 CTGAAGCAAA ACCAGGTGCG GCGGTGACAA ACAGATCTGC GTCTCCGGTC  
 GACTTCGTTT TGGTCCACGC CCGCACTGTT TGTCTAGACG CAGAGGCCAG

33651 TCGCCGCTTA GATCGCTCTG TGTAGTAGTT GTAGTATATC CACTCTCTCA  
 AGCGGCGAAT CTAGCGAGAC ACATCATCAA CATCATATAG GTGAGAGAGT

33701 AAGCATCCAG GCGCCCCCTG GCTTCGGGTT CTATGTAAAC TCCTTCATGC  
 TTCGTAGGTC CGCGGGGGAC CGAAGCCCAA GATACATTTG AGGAAGTAGC

33751 GCCGCTGCC TGATAACATC CACCACCGCA GAATAAGCCA CACCCAGCCA  
 CGGCGACGGG ACTATTGTAG GTGGTGCGGT CTTATTCGGT GTGGGTGCGT

33801 ACCTACACAT TCGTTCTGCG AGTCACACAC GGGAGGAGCG GSAAGAGCTG  
 TGGATGTGTA AGCAAGACGC TCAGTGTGTG CCTCCTCGC CCTTCTCGAC

33851 GAAGAACCAT GTTTTTTTTT TTATTCCAAA AGATTATCCA AAACCTCAAA  
 CTCTTTGGTA CAAAAAATA AATAAGGTTT TCTAATAGGT TTTGGAGTTT

33901 ATGAAGATCT ATTAAGTGAA CGCGCTCCCC TCCGGTGCGG TGGTCAAAT  
 TACTTCTAGA TAATTCACCT GCGCGAGGGG AGGCCACCGC ACCAGTTTGA

FIG. 9A-40

49/70

33951 CTACAGCCAA AGAACAGATA ATGGCATTG TAAGATGTTG CACAATGGCT  
 GATGTCGGTT TCTGTCTAT TACCGTAAAC ATTCTACAAC GTGTTACCGA  
 34001 TCCAAAAGGC AAACGGCCCT CACGTCCAAG TGGACGTAAA GGCTAAACCC  
 AGGTTTTCCG TTTCGCCGGA GTCGAGGTT ACCTGCATT CCGATTTGGG  
 34051 TTCAGGGTGA ATCTCCTCTA TAAACATTCC AGCACCTTCA ACCATGCCCA  
 AAGTCCCACT TAGAGGAGAT ATTTGTAAGG TCGTGGAAGT TGGTACGGGT  
 34101 AATAATTCTC ATCTCGCCAC CTTCTCAATA TATCTCTAAG CAAATCCCGA  
 TTATTAAGAG TAGAGCGGTG GAAGAGTTAT ATAGAGATTG GTTTAGGGCT  
 34151 ATATTAAGTC CGGCCATTGT AAAAATCTGC TCCAGAGCGC CCTCCACCTT  
 TATAATTCAG GCCGTAACA TTTTATAGCG AGGTCTCGCG GGAGGTGGAA  
 34201 CAGCCTCAAG CAGCGAATCA TGATTGCAAA AATTGAGGTT CCTCACAGAC  
 GTCGGAGTTC GTCGTTAGT ACTAACGTTT TTAAGTCCAA GGAGTGTCTG  
 34251 CTGTATAAGA TTCAAAAGCG GAACATTAAAC AAAAATACCG CGATCCCGTA  
 GACATATTCT AAGTTTTGCG CTTGTAATTG TTTTATGCG GCTAGGGCAT  
 34301 GGTCCCTTCG CAGGGCCAGC TGAACATAAT CGTGACGGTC TGCACGGACC  
 CCAGGGAAGC GTCCCAGTCG ACTTGATTTA GCACGTCCAG ACGTGCTGG  
 34351 AGCGCGGCCA CTTCCCCGCC AGGAACCATG ACAAAGAAGC CCACACTGAT  
 TCGCGCCGGT GAAGGGGCGG TCCTTGTAC TGTTCCTTG GGTGTGACTA  
 34401 TATGACACGC ATACTCGGAG CTATGCTAAC CAGCGTAGCC CCGATGTAAG  
 ATACTGTGCG TATGAGCCTC GATACGATTG GTCGCATCGG GGCTACATTG  
 34451 CTTGTTGCAT GGGCGGCGAT ATAAAAATGCA AGGTGCTGCT CAAAAATCA  
 GAACAACGTA CCCGCCGCTA TATTTACGT TCCACGACGA GTTTTTAGT  
 34501 GGCAAGCCCT CGCGCAAAAA AGAAAGCACA TCGTAGTCAT GCTCATGCGA  
 CCGTTTCGGA CGCGTTTTT TCTTTCGTGT AGCATCAGTA CGAGTACGTC  
 34551 ATAAAGGCAG GTAAGCTCCG GAACCACCAC AGAAAAAGAC ACCATTTTTG  
 TATTTCCGTC CATTGAGGC CTTGGTGGT TCTTTTCTG TGGTAAAAAG  
 34601 TCTCAACAT GTCTGCGGGT TTCTGCATAA ACACAAAATA AAATAACAAA  
 AGAGTTTGTA CAGACGCCCA AAGACGTATT TGTGTTTTAT TTTATTGTTT  
 34651 AAAACATTTA AACATTAGAA GCCTGTCCTA CAACAGGAAA AACACCCCTT  
 TTTTGTAAAT TTGTAATCTT CGACAGAAAT GTTGCTCTTT TTGTTGGGAA  
 34701 ATAAGCATAA GACGGACTAC GGCCATGCCG GCGTGACCGT AAAAAAAGT  
 TATTCGTATT CTGCTGATG CCGGTACGGC CGCACTGGCA TTTTITTTGAC  
 34751 GTCACCGTGA TTA AAAAGCA CCACCGACAG CTCCTCGTGC ATGTCGGGAG  
 CAGTGGCACT AATTTTTGCT GGTGGCTGTC GAGGAGCCAG TACAGGCTCT

FIG.9A-41

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34801	TCATAATGTA	AGACTCGGTA	AACACATCAG	GTTGATTCAC	ATCGGTCAGT
	AGTATTACAT	TCTGAGCCAT	TTGTGTAGTC	CAACTAAGTG	TAGCCAGTCA
34851	GCTAAAAAGC	GACCGAAATA	GCCCGGGGGA	ATACATACCC	GCAGGCGTAG
	CGATTTTTTC	CTGGCTTTAT	CGGGCCCCCT	TATGTATGGG	CGTCCGCATC
34901	AGACAACATT	ACAGCCCCCA	TAGGAGGTAT	AACAAAATTA	ATAGGAGAGA
	TCTGTTGTAA	TGTCGGGGGT	ATCCTCCATA	TTGTTTTAAT	TATCCTCTCT
34951	AAAACACATA	AACACCTGAA	AAACCCTCCT	GCCTAGGCAA	AATAGCACCC
	TTTTGTGTAT	TTGTGGACTT	TTTGGGAGGA	CGGATCCGTT	TTATCGTGGG
35001	TCCCGCTCCA	GAACAACATA	CAGCGCTTCC	ACAGCGGCAG	CCATAACAGT
	AGGGCGAGGT	CTTGTTGTAT	GTCGCGAAGG	TGTCGCCGTC	GGTAATTGTCA
35051	CAGCCTTACC	AGTAAAAAAG	AAAACCTATT	AAAAAACAC	CACTCGACAC
	GTCCGAATGG	TCATTTTTTC	TTTTGGATAA	TTTTTTTGTG	GTGAGCTGTG
35101	GGCACCAGCT	CAATCAGTCA	CAGTGTAATA	AAGGGCCAAG	TGCAGAGCGA
	CCGTGGTCCA	GTTAGTCAGT	GTCACATTTT	TTCCCGGTTC	ACGTCTCGCT
35151	GTATATATAG	GACTAAAAAA	TGACGTAACG	GTTAAAGTCC	ACAAAAAACA
	CATATATATC	CTGATTTTTT	ACTGCATTGC	CAATTCAGG	TGTTTTTTGT
35201	CCCAGAAAAA	CGCACGCGAA	CCTACGCCCA	GAAACGAAAG	CCAAAAAAC
	GGGTCTTTTT	GCGTGCGCTT	GGATGCGGGT	CTTTGCTTTC	GGTTTTTTGG
35251	CACAACCTCC	TCAAATCGTC	ACTTCCGTTT	TCCCACGTTA	CGTCACITCC
	GTGTTGAAGG	AGTTTAGCAG	TGAAGGCAAA	AGGGTGCAAT	GCAGTGAAGG
35301	CATTTTAAGA	AAACTACAAT	TCCCAACACA	TACAAGTTAC	TCCGCCCTAA
	GTAAAAATCT	TTTGATGTTA	AGGGTTGTGT	ATGTTCAATG	AGGCGGGATT
35351	AACCTACGTC	ACCCGCCCCG	TTCCACGCGC	CCGCGCCACG	TCACAAACTC
	TTGGATGCAG	TGGGCGGGGC	AAGGGTGCGG	GGCGCGGTGC	AGTGTTTTGA
35401	CACCCCTCA	TTATCATATT	GGCTTCAATC	CAAAATAAGG	TATATTATTG
	GTGGGGGAGT	AATAGTATAA	CCGAAGTTAG	GTTTATTATC	ATATAATAAC

PacI

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35451	ATGATGTTAA	TTAAGAAATC	GGATCTGCGA	CGCGAGGCTG	GATGGCCTTC
	TACTACAATT	AATTCTTAAG	CCTAGACGCT	CGCTCCGAC	CTACCGGAAG
35501	CCCATTATGA	TTCTTCTCGC	TTCCGGCGGC	ATCGGGATGC	CCGCGTTGCA
	GGGTAACTACT	AAGAAGAGCG	AAGGCCCGCG	TAGCCCTACG	GGCGCAACGT
35551	GGCCATGCTG	TCCAGGCAGG	TAGATGACGA	CCATCAGGGA	CAGCTTCAAG
	CCGGTACGAC	AGTCCGTCC	ATCTACTGCT	GGTAGTCCCT	GTCGAAGTTC

FIG.9A-42

51/70

35601 GCCAGCAAAA GCCCAGGAAC CGTAAAAAGG CCGCGTTGCT GCGGTTTTTC  
 CGGTCTTTTT CCGGTCCTTG GCATTTTTTC GCGCAACGA CCGCAAAAAA  
 35651 CATAGGCTCC GCCCCCCTGA CGAGCATCAC AAAAATCGAC GCTCAAGTCA  
 GTATCCGAGG CGGGGGGACT GCTCGTAGTG TTTTATAGCTG CGAGTTCAGT  
 35701 GAGGTGGCGA AACCCGACAG GACTATAAAG ATACCAGGCG TTTCCCCCTG  
 CTCCACCGCT TTGGGCTGTC CTGATATTC TATGGTCGCG AAAGGGGAC  
 35751 GAAGCTCCCT CGTGCCTCT CCGTGTCCGA CCCTGCCGCT TACCGGATAC  
 CTTGAGGGA GCACGCAGA GGACAAGGCT GGGACGGCGA ATGGCTATAG  
 35801 CTGTCCGCCT TTCTCCCTTC GGAAGCGGTG GCGCTTTCTC ATAGCTCAGG  
 GACAGGCGGA AAGAGGGAAG CCTTCGCAC CCGCAAAAGG TATCGAGTGC  
 35851 CTGTAGGTAT CTCAGTTCGG TGTAAGTCTG TCGCTCCAAG CTGGGCTGTG  
 GACATCCATA GAGTCAAGCC ACATCCAGCA AGCGAGGTTC GACCCGACAC  
 35901 TGCACGAACC CCCCGTTTCA CCCGACCGCT GCGCCTTATC CGGTAACAT  
 ACGTGCTTGG GGGGCAAGTC GGGCTGGCGA CCGGAATAG GCCATTGATA  
 35951 CGTCTTGAGT CCAACCCGGT AAGACACGAC TTATCGCCAC TGGCAGCAGC  
 GCAGAACTCA GGTGCGCCA TTCTGTGCTG AATAGCGGTG ACCGTGCTCG  
 36001 CACTGGTAAC AGGATTAGCA GAGCGAGGTA TGTAAGCGGT GCTACAGAGT  
 GTGACCATTG TCCTAATCGT CTCGCTCCAT ACATCCGCCA CGATGTCTCA  
 36051 TCTTGAAGTG GTGGCCTAAC TACGGCTACA CTAGAAGGAC AGTATTTGGT  
 AGAACTTCAC CACCGGATTG ATGCCGATGT GATCTTCCTG TCATAAACCA  
 36101 ATCTGCGCTC TGCTGAAGCC AGTTACCTTC GGA AAAAGAG TTGSTATGCTC  
 TAGACGCGAG ACGACTTCGG TCAATGSAAG CCTTTTCTC AACCATCGAG  
 36151 TTGATCCGGC AAACAAACCA CCGCTGGTAG CGGTGGTTTT TTTGTTTGCA  
 AACTAGGCCG TTGTTTGGT GCGCACCATC GCCACCAAAA AAACAAACGT  
 36201 AGCAGCAGAT TACGCGCAGA AAAAAGGAT CTCAAGAAGA TCCTTTGATC  
 TCGTGTCTA ATGCGCGTCT TTTTCTCTA GAGTCTTCT AGGAAACTAG  
 36251 TTTTCTACGG GGTCTGACGC TCAGTGAAC GAAAACTCAC GTTAAGGGAT  
 AAAAGATGCC CCAGACTGCG AGTCACCTTG CTTTGTAGTG CAATTCCCTA  
 36301 TTTGGTCATG AGATTATCAA AAAGGATCTT CACCTAGATC CTTTAAATC  
 AAACAGTAC TCTAATAGTT TTCTTAGAA GTGGATCTAG GAAAAATTAG  
 36351 AATCTAAAGT ATATATGAGT AAAGTTGGTC TGACAGTTAC CAATGCTTAA  
 TTAGATTTC TATATACTCA TTGCAACGAG ACTGTCAATG GTTACGAAAT  
 36401 TCAGTGAGGC ACCTATCTCA GCGATCTGTC TATTTCTGTC ATCCATAGTT  
 AGTCACTCCG TGGATAGAGT CGCTAGACAG ATAAAGCAAG TAGGTATCAAA

FIG.9A-43

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36451 GCCTGACTCC CGTCTGTGA GATAACTACG ATACGGGAGG GCTTACCATC  
 CGGACTGAGG GGCAGCACAT CTATTGATGC TATGCCCTCC CGAATGGTAG  
 36501 TGGCCCCAGT GCTGCAATGA TACCGCGAGA CCCACGCTCA CCGGCTCCAG  
 ACCGGGGTCA CGACGTACT ATGGCGCTCT GGGTGCAGT GCGCGAGGTC  
 36551 ATTTTACAGC AATAAACAG CCAGCCGGAA GGGCCGAGCG CAGAAGTGGT  
 TAAATAGTCG TTATTTGGTC GGTCTGGCCTT CCGGCTCGC GTCTTCACCA  
 36601 CCTGCAACTT TATCGCCCTC CATCCAGTCT ATTAATTGTT GCCGGGAAGC  
 GGACGTTGAA ATAGCGGAG GTAGGTCAGA TAATTAACAA CGGCCCTTCG  
 36651 TAGAGTAAGT AGTTCGCCAG TTAATAGTTT GCGCAACGTT GTTGCCATTG  
 ATCTCATTCA TCAAGCGGTC AATTATCAAA CGCGTTGCAA CAACGGTAAC  
 36701 CTACAGGCAT CGTGGTGTCA CGCTCGTCGT TTGGTATGGC TTCAATTCAGC  
 GATGTCCGTA GCACCACAGT GCGAGCAGCA AACCATACCG AAGTAAGTCG  
 36751 TCCGGTCCC AACGATCAAG GCGAGTTACA TGATCCCCCA TGTGTGCAA  
 AGGCCAAGGG TTGCTAGTTC CGCTCAATGT ACTAGGGGGT ACAACACGTT  
 36801 AAAAGCGGTT AGCTCCTTCG GTCTCCGAT CGTTGTGAGA AGTAAGTTGG  
 TTTTCGCCAA TCGAGGAAGC CAGGAGGCTA GCAACAGTCT TCATTCAACC  
 36851 CCGCAGTGTT ATCACTCATG GTTATGGCAG CACTGCATAA TTCTCTTACT  
 GGCGTCACAA TAGTGAGTAC CAATACCGTC GTGACGTATT AAGAGAATGA  
 36901 GTCATGCCAT CCGTAAGATG CTTTTCTGTG ACTGGTGAGT ACTCAACCAA  
 CAGTACGGTA GGCATTCTAC GAAAAGACAC TGACCACTCA TGAGTTGGTT  
 36951 GTCATTCTGA GAATAGTGTA TGGGCGGACC GAGTTGCTCT TGCCCGGCGT  
 CAGTAAGACT CTTATCACAT ACGCCGCTGG CTCAACGAGA ACGGGCCGCA  
 37001 CAACACGGGA TAATACCGCG CCACATAGCA GAACTTTAAA AGTGCTCATC  
 GTTGTGCCCT ATTATGGCGC GGTGTATCGT CTTGAAATTT TACGAGTAG  
 37051 ATTGAAAAAC GTTCTTCGGG GCGAAAACTC TCAAGGATCT TACCGTGT  
 TAACCTTTTT CAAGAAGCCC CGCTTTTGAG AGTTCCTAGA ATGGCGACAA  
 37101 GAGATCCAGT TCGATGTAAC CCACTCGTGC ACCCAACTGA TCTTCAGCAT  
 CTCTAGGTCA AGCTACATTG GGTGAGCAGC TGGGTTGACT AGAAGTCGTA  
 37151 CTTTTACTTT CACCAGCGTT TCTGGGTGAG CAAAACAGG AAGGCAAAAT  
 GAAAATGAAA GTGGTGCAA AGACCACTC GTTTTTGTCC TTCCGTTTTA  
 37201 GCCGCAAAA AGGGAATAAG GGCACACCGG AAATGTTGAA TACTCATACT  
 CGCGGTTTTT TCCCTTATTG CCGCTGTGCC TTTACAACCT ATGAGTATGA  
 37251 CTTCCTTTTT CAATATTATT GAAGCATTTA TCAGGGTTAT TGTCTCATGA  
 GAAGGAAAAA GTTATAATAA CTTCGTAAT AGTCCCAATA ACAGAGTACT

FIG.9A-44

53/70

37301 GCGGATACAT ATTTGAATGT ATTTAGAAAA ATAAACAAAT AGGGGTTCGG  
CGCCTATGTA TAAACTTACA TAAATCTTTT TATTTGTTTA TCCCAAGGC

37351 CGCACATTTT CCCGAAAAGT GCCACCTGAC GTCTAAGAAA CCATTATTAT  
GCGTGTAAGG GGGCTTTTCA CGGTGGACTG CAGATTCTTT GGTAAATAATA

37401 CATGACATTA ACCTATAAAA ATAGGCGTAT CACGAGGCC TTTGTCCTTC  
GTA CTGTAAT TGGATAATTT TATCCGCATA GTGCTCCGGG AAAGCAGAAG

37451 AAGAATTGGA TCCGAATTCT TAAT  
TTCTTAACCT AGGCTTAAGA ATTA

FIG.9A-45

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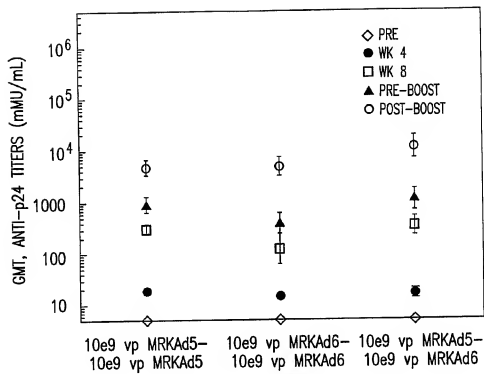


FIG.10

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1 CATCATCAAT AATATACCTT ATTTTGGATT GAAGCCAATA TGATAATGAG GGGGTGGAAT  
 61 TTGTGACGTG GCGCGGGGCG TGGGAACGGG GCGGGTGACG TAGTAGTGTG GCGGAAGTGT  
 121 GATGTTGTAA GTGTGCGGGA ACACATGTAA GCGCCGGATG TGGTAAAGT GACGTTTTTG  
 181 GTGTGCGCGG GTGTACACGG GAAGTGACAA TTTTCGCGCG GTTTTAGGGC GATGTTGTAG  
 241 TAAATTTGGG CGTAACCAAG TAATATTTGG CCAATTTTCGC GGGAAAACTG AATAAGAGGA  
 301 AGTGAATCT GAATAATCTT GTGTACTCA TAGCGCGTAA TATTTGTCTA TTTTGTCTA  
 361 GACTTTGACC GTTTACGTGG AGACTGCCCC AGGTGTTTTT CTCAGGTGTT TTCCGCGTTC  
 421 CGGGTCAAAG TTGGCGTTTT ATTATTATAG TCAGCTGACG CGCAGTGTAT TTATACCCGG  
 481 TGAGTTCCTC AAGAGGCCAC TCTTGAGTGC CAGCGAGTAG AGTTTTCTCC TCCGAGCCGG  
 541 TCCGACACCG GGACTGAAAA TGAGACATAT TATCTGCCAC GGAGGTGTTA TTACCGAAGA  
 601 AATGGCCGCC AGTCTTTTGG ACCAGCTGAT CGAAGAGGTA CTGGCTGATA ATCTTCCACC  
 661 GACTTTGACC GTTTAACCAC CTACCCCTCA CGAACTGTAT GATTTAGACG TGACGGCCCC  
 721 CGAAGATCCC AACGAGGAGG CGGTTTCGCA GATTTTCCCG GAGTCTGTAA TGTGTGCGGT  
 781 GCAGGAAGGG ATTGACTTAT TCACTTTTCC GCGGCGGCCG GGTCTCCGG AGCCGCTCA  
 841 CCTTTCCCGG CAGCCCGAGC AGCCGGAGCA GAGAGCCTTG GGTCCGGTTT CTATGCCAAA  
 901 CCTTGTGCGC GAGGTGATCG ATCTTACCTG CCACGAGGCT GGTCTTCCAC CCAGTGAGCA  
 961 CGAGGATGAA GAGGGTGAGG AGTTTGTGTT AGATTATGTG GAGCACCCCG GGCACGGTTG  
 1021 CAGGTCTTGT CATTATCACC GGAGGAATAC GGGGACCCA GATATTATGT GTTCGCTTTG  
 1081 CTATATGAGG ACCTGTGGCA TGTTTGTCTA CAGTAAGTGA AAAATTATGG CGAGTGGGTG  
 1141 ATAGAGTGGT GGGTTTGGTG TGGTAATTTT TTTTATAATT TTTACAGTTT TGTGGTTTAA  
 1201 AGAATTTTGT ATTTGTGATT TTTAAAAGGT CCTGTGTCTG AACCTGAGCC TGAGCCGAGT  
 1261 CCAGAACCAG AGCCTGCAAG ACCTACCCGG CGTCTAAAT TGGTGCTCG TATCCTGAGA  
 1321 CGCCCGACAT CACCTGTGTC TAGAGAAATG AATAGTAGTA CGATAGCTG TGACTCCGGT  
 1381 CCTTCTAACA CACCTCTGTA GATACACCCG GTGGTCCCGC TGTGCCCAT TAAACCAAGT  
 1441 GCGCTGAGAG TTGGTGGGCG TCGCCAGGCT GTGGAATGTA TCGAGGAGT GCTTAACGAG  
 1501 TCTGGGCAAC CTTTGGACTT GAGCTGTAAA CGCCCAAGCG CATAGGTGT AAACCTGTGA  
 1561 TTGCGTGTGT GGTAAACGCC TTTGTTTGCT GAATGAGTTG ATGTAAGTTT AATAAAGGGT  
 1621 GAGATAATGT TTAACCTGCA TGGCGTGTTA AATGGGCGGG GGTCTAAAGG GTATATAATG  
 1681 CGCCGTGGGC TAATCTTGGT TACATCTGAC CTCATGGAGG CTTGGGAGTG TTTGGAAGAT  
 1741 TTTTCTGCTG TCGCTAAGT GCTGGAACAG AGCTCTAACA GTACCTCTTG GTTTTGGAGG  
 1801 TTTCTGTGGG GCTCCTCCCA GGCAAGGTTA GTCTGCAGAA TTAAGGAGGA TTACAAGTGG  
 1861 GAAITTTGAA AGCTTTTGAA ATCCTGTGGT GAGCTGTTTG ATTCCTTGAA TCTGGGTAC  
 1921 CAGGCGCTTT TCCAAGAGAA GGTATCAAG ACTTTGGATT TTTCCACACC GGGGCGCGCT  
 1981 GCGGCTGCTG TTGCTTTTTT GAGTTTTATA AAGGATAAAT GGAGCGAAGA AACCCATCTG  
 2041 AGCGGGGGGT ACCTGCTGGA TTTTCTGGCC ATGCATCTGT GGAGAGCGGT GGAGACACAC  
 2101 AAGAATCGCC TGCTACTGTT GTCTTCCGTC CGCCCGGCAA TAATACCGAC GGAGGAGCAA  
 2161 CAGCAGGAGG AAGCCAGGCG GCGCGGGCGG CAGGAGCAGA GCCCATGGAA CCCGAGAGCC  
 2221 GGCCTGAGCC CTCGGGAATG AATGTTGTAC AGGTGGCTGA ACTGTTTCCA GAACTAGAGT  
 2281 GCATTTTAAC CATTAAACGAG GATGGGCAGG GGCTAAAGGG GGTAAAGAGG GAGCGGGGCT  
 2341 CTTCTGAGCG TACAGAGGAG GCTAGGAATC TAACTTTTAG CTTAATGACC AGACACCGTC  
 2401 CTGAGTGTGT TACTTTTCAG CAGATTAAAG ATAATTGCGC TAATGAGCTT TAATGAGCTT  
 2461 CGCAGAAAGT TTCCATAGAG CAGCTGACCA CTACTGGCT GCAGCCAGGG GATGATTTTG  
 2521 AGGAGGCTAT TAGGGTATAT GCAAGGTTGG CACTTAGGCC AGATTGCAAG TACAAGATTG  
 2581 GCAAACCTGT AAATATCAGG AATTGTTGCT ACATTTCTGG GAACGGGGCC GAGGTGAGA  
 2641 TAGATACGGA GGATAGGGTG GCCTTTAGAT GTAGCATGAT AAATATGTGG CCGGGGGTGC

FIG. 11A-1

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2701	TTGGCATGGA	CGGGGTGGTT	ATTATGAATG	TGAGGTTTAC	TGGTCCCAAT	TTTAGCGGTA
2761	CGGTTTTCT	GGCCAATACC	AATCTTATCC	TACACGGTGT	AAGCTTCTAT	GGGTTTAAACA
2821	ATACCTGTGT	GGAGGCGCTGG	ACCGATGTAA	GGGTTCCGGG	CTGTGCCTTT	TACTGTCTGT
2881	GGAGGGGGGT	GGTGTGTGCG	CCCAAAAGCA	GGGCTTCAAT	TAAGAAAATGC	CTGTTTGGAAA
2941	GGTGTACCTT	GGGTATCCCTG	TCTGAGGGTA	ACTCCAGGGT	GCGCCACAAT	GTGGCCTCCG
3001	ACTGTGGTTG	CTTTATGCTA	GTGAAAACGC	TGGCTGTGAT	TAAGCATATC	ATTGGTGTGTG
3061	GCAACTGCGA	GGACAGGGCC	TCTCAGATGC	TGACCTGCTC	GGACGGCAAC	TGTCACTTGC
3121	TGAAGACCAT	TCACGTAGCC	AGCCACTCTC	GCAAGGCGTG	GCCAGTGTTT	GAGCACAAACA
3181	TACTGACCCG	CTGTTCCCTTG	CATTTGGGTA	ACAGGAGGGG	GGTGTTCCTA	CCTTACCAAT
3241	GCAATTTGAG	TCACACTAAG	ATATTGCTTG	AGCCCGAGAG	CATGTCCAAG	GTGAACCTGA
3301	ACGGGGTGT	TGACATGACC	ATGAAGATCT	GGAAAGTGCT	GAGGTACGAT	GAGACCCGCA
3361	CCAGGTGCAG	ACCTTGCAG	TGTGGCGGTA	AACATATTAG	GAACCAAGCT	GTGATGCTGG
3421	ATGTGACCGA	GGAGCTGAGG	CCCGATCACT	TGGTGTGCG	CTGCACCCGC	GCTGAGTTTG
3481	GCTCTAGCGA	TGAAGATACA	GATTGAGGTA	CTGAAATGTG	TGGGCGTGGC	TAAAGGGTGG
3541	GAAAGAATAT	ATAAGGTGGG	GGTCTCATGT	AGTTTTGTAT	CTGTTTTGCA	GCAGCCGCCG
3601	CCATGAGCGC	CAACTCGTTT	GATGGAAGCA	TTGTGAGCTC	ATATTTGACA	ACGCCGATGC
3661	CCCCATGGGC	CGGGGTGCGT	CAGAATGTGA	TGGCTCCAG	CATTGATGGT	GCGCCCTCC
3721	TGCCCGCAAA	CTCTACTACC	TTGACCTACG	AGACCGTGT	TGGAACGCCG	TTGGAGACTG
3781	CAGCCTCCGC	CGCCGCTTCA	GCCGCTGCAG	CCACCGCCCG	CGGGATTGTG	ACTGACTTTG
3841	CTTTCTTGAG	CCCGCTTGA	AGCAGTGCAG	CTTCCCGTTC	ATCCGCCCGC	GATGACAAGT
3901	TGACGGCTCT	TTTGGCAAAA	TTGGATTCTT	TGACCCGGGA	ACTTAATGTC	GTTTCTCAGC
3961	AGCTGTTGGA	TCTGCGCCAG	CAGGTTTTCTG	CCCTGAAGGC	TTCTCCCTCC	CCCAATGCCG
4021	TTTAAACAT	AAATAAAAAAC	CAGACTCTGT	TTGGATTGG	ATCAAGCAAG	TGCTTTGCTG
4081	TCTTTTATTTA	GGGGTTTTG	GCGCGCCGTA	GGCCCGGAG	CAGCGGTCTC	GGTCTGTGAG
4141	GGTCTGTGT	ATTTTTTCCA	GGACGTGGTA	AAGGTGACT	TGGATTTCA	GATACATGGG
4201	CATAAGCCCG	TCTCTGGGGT	GGAGGTAGCA	CCAATGCAGA	GCTTCATGCT	CGGGGGTGGT
4261	GTTGTAGATG	ATCCAGTCTG	AGCAGGAGCG	CTGGGCGTGG	TGCCATAAAA	TGCTTTTACG
4321	TAGCAAGCTG	ATTGCCAGGG	GCAGGCCCTT	GGTGAAGTG	TTTACAAGAG	GGTTAAGCTG
4381	GGATGGGTGC	ATACGTGGGG	ATATGAGATG	CATCTTGGAG	TGTAATTTTA	GGTGGCTAT
4441	GTTCCCAAGC	ATATCCCTCC	GGGGATTCAAT	GTTGTGCAGA	ACCACCAAGCA	CAGTGTATCC
4501	GGTGCACCTG	GGAAATTTGT	CATGTAGCTT	AGAAGGAAAT	GCGTGGAAGA	ACTTGGAGAC
4561	GCCCTTGTGA	CCTCCAAGAT	TTTCCATGCA	TTCTGTCATA	ATGATGGCAA	TGGGCCACG
4621	GGCGGGGGCC	TGGCGAAGA	TATTTCTGGG	ATCACTAACG	TCATAGTTGT	GTTCAGGAT
4681	GAGATCGTCA	TAGGCCATTT	TTACAAAGCG	CGGGCGGAGG	GTGCCAGACT	CGGGTATAAT
4741	GGTTCCATCC	GGCCACGGGG	CGTAGTTACC	CTCACAGATT	TGCAATTTCC	AGCGTTTGAG
4801	TTACAGATGG	GGGATCATGT	CTACCTGCGG	GGCGATGAAG	AAAACCGTTT	CCGGGGTAGG
4861	GGAGATCAGC	TGGGAAGAAA	GCAGGTTTCT	AAGCAGCTGC	GACTTACCGC	AGCCGGTGGG
4921	CCCGTAAATC	ACACCTATTA	CCGGCTGCAA	CTGGTAGTTA	AGAGAGCTGC	AGCTACGGGC
4981	ATCCCTGAGC	AGGGGGGCCA	CTTCGTAAAG	CATGTCCCTG	ACTTGCAATG	TTTCCTGATC
5041	CAAAATCCGC	AGAAGGCGCT	CGCCGCCAG	CGATAGCAGT	TCTTGAACGG	AAGCAAGTTC
5101	TTTCAACGGT	TTGAGGCGGT	CGCCCGTAGG	CATGCTTTTG	AGCGTTTGAC	CAAGCAGTTC
5161	CAGGCGGTCC	CACAGCTCGG	TCACGTGCTC	TACGGCATCT	CGATCCAGCA	TATCTCCTCG
5221	TTTCGCGGGT	TGGGGCGGCT	TTGCTGTATC	TGCAGTAGTC	GGTGCTCGTC	CAGACGGGCC
5281	AGGGTCATGT	CTTTCACAGG	GCAGAGGGTC	CTGCTACAGG	TAGTCTGGGT	CACGGTGAAG
5341	GGGTGCGCTC	CGGGTTGCGC	GCTGCGCAGG	GTGCGCTTGA	GGCTGGTCTT	GCTGGTGCTG

FIG. 11A-2

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5401	AAGCGCTGCC	GGTCTTCGCC	CTGCGCGTCG	GCCAGGTAGC	ATTTGACCAT	GGTGTCATAG
5461	TCCAGCCCT	CCGCGCGGTG	GCCCTTGCGG	CGCAGCTTGC	CCTTGAGGGA	GGCGCCGCAC
5521	GAGGGGAGCT	GCAGACTTTT	AAGGGCGTAG	AGCTTGGGCG	CGAGAAATAC	CGATTCCGGG
5581	GAGGTAGCAT	CCGCGCCGCA	GGCCCCGCAG	ACGGTCTCGC	ATTCCACGAG	CCAGGTGAGC
5641	TCTGCCCGTT	CGGGGTCAAA	AACCAGGTIT	CCCCCATGCT	TTTTGATGCG	TTTCTTAACCT
5701	CTGGTTTCCA	TGAGCCGGTG	TCCACGCTCG	GTGACGAAAA	GGCTGTCCGT	GTCCCCGTAT
5761	ACAGACTTGA	GAGGCTCTGC	CTCGAGCGGT	GTTCGCGGT	CCTCTCTGTA	TAGAAACTCG
5821	GACCACTCTG	AGACGAAGGC	TCGCGTCCAG	GCCAGCAGCA	AGGAGGCTAA	GTGGGAGGGG
5881	TAGCGGTCTG	TGTCCACTAG	GGGGTCCACT	CGCTCCAGGG	TGTGAAGACA	CATGTGCCCC
5941	TCTTCGCGAT	CAAGGAAGGT	GATTGGTTTA	TAGGTGTAGG	CCACGTGACC	GGGTGTCTCT
6001	GAAGGGGGGG	TATAAAAGGG	GGTGGGGGGG	CGTTGCTCCT	CACCTCTCTC	CGCATCGCTG
6061	TCTCGAGGG	CCAGCTGTTG	GGGTGAGTAC	TCCCTCTCAA	AAGCGGGCAT	GACTTCTGCG
6121	CTAAGATTGT	CAGTTTCCAA	AAACGAGGAG	GATTTGATAT	TCACCTGGCC	CGCGGTGATG
6181	CCTTTGAAGG	TGGCCGCGTC	CATCTGGTCA	GAAGAGACAA	TCTTTTGTTT	GTCAAGCTTG
6241	GTGGCAACAG	ACCCGTAGAG	GGCGTTGGAC	AGCAACTTGG	CGATGGAGCG	CAGGGTTTGG
6301	TTTTTGTGCG	GATCGGCGCG	CTCCTTGGCC	CGGATGTTTA	GCTGCACGTA	TTGCGCGCGA
6361	ACGCACCGCC	ATTCGGGAAA	GACGGTGGTG	CGCTCGTCGG	GCACCTAGTG	CACGCGCCAA
6421	CCGCGGTTGT	CGAGGGTGAC	AAGGTCAACG	CTGGTGGCTA	CCTCTCCGCG	TAGGCGCTCG
6481	TTGGTCCAGC	AGAGGCGGCC	GCCCTTGCGC	GAGCAGAATG	GCGGTAGTGG	GTCTAGCTGC
6541	GTCTCGTCGG	GGGGGTCTGC	GTCCACGGTA	AAGACCCCGG	CGACGAGGCG	CGCGTCGAAG
6601	TAGTCTATCT	TGCATCTTTG	CAAGTCTAGC	GCCTGCTGCC	ATGCGCGGGG	GGCAAGCGCG
6661	CGCTCGTATG	GGTTGAGTGG	GGGACCCCAT	GGCATGGGGT	GGGTGAGCGC	GGAGGCGTAC
6721	ATGCCGCAAA	TGTCGTAAAC	GTAGAGGGGC	TCTTGAGTA	TTCCAAGATA	TGTAGGGTAG
6781	CATCTTCCAC	CGCGGATGCT	GGCGCGCACG	TAATCGTATA	GTTCGTGCGA	GGGAGCGGAG
6841	AGGTCGGGAC	CGAGGTTGCT	ACGGCGGGGC	TGCTCTGCTC	GGAAAGCTAT	CTGCGCTGAAG
6901	ATGGCATGTG	AGTTGGATGA	TATGGTTGGA	CGCTGGAAGA	CGTTGAAGCT	GGCGTCTGTG
6961	AGACCTACCG	CGTCACGCA	GAAGGAGGCG	TAGGAGTCGC	GCAGCTTGTT	GACCAGCTCG
7021	CGGGTGACCT	GCACGTCTAG	GGCGCAGTAG	TCCAGGGTTT	CCTTGATGAT	GTCTACATTA
7081	TCCTGTCCCT	TTTTTTTCCA	CAGCTCGCGG	TTGAGGACAA	ACTCTTCGCG	GCTTTTCCAG
7141	TACTCTTGGA	TCGGAACCC	GTCGGCCCTC	GAACGGAAG	AGCCTAGCAT	GTAGCACTGG
7201	TTGACGGGCT	GGTAGGCGCA	GCATCCCTTT	TCTACGGGTA	CGCGGTATGC	CTGCGCGGCC
7261	TTCCGGGAGG	AGGTGTGGGT	GAGCGCAAG	GTGTCCCTAA	CCATGACCTT	GAGGTACTGG
7321	TATTTGAAGT	CAGTGTGCTC	GCATCCGCC	TGCTCCGAGA	GCAAAAAGTC	CGTGGCGTTT
7381	TTGGAACGCG	GGTTTGGCAG	GGCGAAGGTG	ACATCGTTGA	AGAGTATCTT	TCCCGCGCGA
7441	GGCATAAAGT	TGCGTGTGAT	CGGGAAGGGT	CCCGGCACCT	CGGAACGGTT	GTAAATTACC
7501	TGGGCGGCGA	GCACGATCTC	GTCAAAGCCG	TTGATGTTGT	GGCCCAACAAT	GTAAAGTTCC
7561	AAGAAGCGCG	GGATGCCCTT	GATGGAAGGC	AATTTTTTAA	GTTCCTCGTA	GGTGAGCTCT
7621	TCAGGGGAGC	TGAGCCCGTG	CTCTGAAAGG	GCCAGTCTG	CAAGATGAGG	TTGGAAGCG
7681	ACGAATGAGC	TCCACAGGTC	ACGGGCCATT	AGCATTTGCA	GGTGGTCGCG	AAAGGTCCTA
7741	AACTGGCGAC	CTATGGCCAT	TTTTTCTGGG	GTGATGCAGT	AGAAAGGTAAG	CGGGTCTTGT
7801	TCCAGGCGGT	CCCATCCAA	GTCGCCGGCT	AGGTCTCGCG	CGCGGTGCAC	TAGAGGCTCA
7861	TCTCCGCGCA	ACTTCATGAC	CAGCATGAAG	GGCAGGAGCT	GCTTCCCAAA	GGCCCCCATC
7921	CAAGTATAGG	TCTCTACATC	GTAGGTGACA	AAGAGACGCT	CGGTGCGAGG	ATTGGAAGCG
7981	ATCGGGAAGA	ACTGGATCTC	CCGCGACCAG	TGGGAGGAGT	GGCTGTTGAT	GTGGTGAAAG
8041	TAGAAGTCCC	TGGCAGCGGC	CGAACACTCG	TGCTGGCTTT	TGTAAAGACG	TGCGCAGTAC

FIG. 11A-3

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8101	TGGCAGCGGT	GCACGGGCTG	TACATCTGCT	ACGAGGTTGA	CCTGACGACC	GCGCACAAGG
8161	AAGCAGAGTG	GGAAITTTGAG	CCCCTCGCCT	GGCGGGTTTG	GCTGGTGGTC	TTCTACTTCG
8221	GCTGCTTTGTC	CTTGACCCTC	TGGCTGCTCG	AGGGAGGTTA	CGGTGGATCG	GACCACCAGG
8281	CGCGCGGAGC	CCAAAGTCCA	GATGTCCGCG	CGCGCGGGTC	GGAGCTTGAT	GACAACATCG
8341	CGCAGATGGG	AGCTGTCCAT	GGTCTGGAGC	TCCGCGGGCT	TCAGGTTCAGG	CGGGAGCTCC
8401	TGCAGGTTTA	CCTCGCATAG	CCGGGTCAAG	GGCGGGGCTA	GGTCCAGGTG	ATACCTGATT
8461	TCCAGGGGCT	GGTTGGTGGC	GGCGTGCATG	GCTTGCAAGA	GGCCGCATCC	CCGGCGCGCG
8521	ACTACGGTAC	CGCGCGGCGG	CGCGTGGGCC	CGGGGGGTGT	CCTTGGATGA	TGCATCTAAA
8581	AGCGGTGACG	CGGGCGGGCC	CCCGAGGGTA	GGGGGGGCTC	GGGACCCGCC	GGGAGAGGGG
8641	GCAGGGGCAC	GTGCGCGCGG	CGCGGGGCA	GGAGCTGGTG	CTGCGCGCGG	AGGTTGCTGG
8701	CGAACGCGAC	GACGCGGCGG	TTGATCTCCT	GAATCTGGCG	CCTCTGCGTG	AAGACGACGG
8761	CGCCGGTGAG	CTTGAACCTG	AAAGAGAGTT	CGACAGAATC	AATTTCCGTG	TCGTTGACGG
8821	CGGCTTGGCG	CAAAATCTCC	TGCACGTCTC	CTGAGTTGTC	TTGATAGGCG	ATCTCGGCCA
8881	TGAAGCTGCT	GATCTCTTCC	TCCTGGAGAT	CTCCGCGTCC	GGCTCGCTCC	ACGGTGGCGG
8941	CGAGTCTGTT	GGAGATGCGG	GCCATGAGCT	GGGAGAAGGC	GTGAGGGCTC	CCCTCGTTCC
9001	AGACGCGGCT	GTAGACCACG	CCCCCTTCGG	CATCGCGGGC	CGCGATGACC	ACCTGCGGCA
9061	GATTGAGCTC	CACGTGCCGG	CGGAAGACGG	CGTAGTTTCC	CAGGCGCTGA	AAGAGGTAGT
9121	TGAGGGTGGT	GGCGGTGTGT	TCTGCCACGA	AGAAGTACAT	AACCAAGCGC	CGCAACGTGG
9181	ATTGCTTGAT	ATCCCCCAAG	GCCTCAAGGC	GCTCCATGGC	CTCGTAGAAG	TCCACGGCGA
9241	AGTTGAAATAT	CTGGGAGTTG	CGCGCCGACA	CGGTTAACTC	CTCTCCGAGA	AGACGGATGA
9301	GCTCGGCGAC	AGTGTGCGCG	ACCTCGCGCT	CAAAGGCTAC	AGGGGCTCTC	TCTTCTCTTT
9361	CAATCTCCTC	TTCATAAAGG	GCCTCCCTTT	CTTCTTCTTC	TGGCGGCGGT	GGGGAGGGGG
9421	GGACACGGCG	CGGACGACGG	CGCACGGGA	GGCGGTGACG	AAAGCGCTCG	ATCATCTCCC
9481	CGCGGCGACG	CGCATGGTCC	TCGGTGACGG	CGCGCCGCTT	CTCGCGGGGG	CGCAGTTGGA
9541	AGACGCGCCG	CGTCATGTCC	CGGTTATGGG	TTGGCGGGGG	GCTGCCGTGC	GGCAGGGATA
9601	CGCGCTAAC	GATGCATCTC	AACAATTGTT	GTGTAGGTAC	TCCGCCACCG	AGGGACCTGA
9661	CGGAGTCCGC	ATCGACCGGA	TCGGAAAACC	TCTCGAGAAA	GGCGTCTAAC	CAGTCAAGT
9721	CGCAAGGTAG	GCTGAGCACC	GTGGCGGGCG	GCAGCGGGCG	CGGTCGGGGG	TTGTTTCTGG
9781	CGGAGGTGCT	GCTGATGATG	TAATTAAGAAT	AGGCGGTCTT	GAGACGGGCG	ATGGTCGACA
9841	GAAGCACCAT	GTCTTGGGTT	CGGCTCTGCT	GAATGCGCAG	CGGTCGGGCC	ATGCCCCAGG
9901	CTTCGTTTTG	ACATCGGGCG	AGGCTTTTGT	AGTAGTCTTG	CATGAGCCTT	TCTACCGGCA
9961	CTTCTTCTTC	TCCTTCTCTC	TGTCTCGCAT	CTCTTGCATC	TATCGCTGGG	CGGGCGGCGG
10021	AGTTTGGCCG	TAGGTTGGCG	CCCTTCTCTC	CCATCGGTGT	GACCCCGAAG	CCCTCATCTG
10081	GCTGAAGCAG	GGCCAGGTCG	CGGACAACGC	GCTCGGCTAA	TATGGCTCGC	TGCACCTGCG
10141	TGAGGGTAGA	CTGGAAGTCG	TCATGTGCCA	CAAAGCGGTG	GTATGCGGCC	GTGTTGATGG
10201	TGTAAGTGCA	GTGGGCCATA	ACGGACCAAGT	TAACGGTCTG	GTGACCGCGG	TGCGAGAGCT
10261	CGGTGTACCT	GAGACGCGAG	TAAGCCCTTG	AGTCAAAGAC	GTAGTCTGTTG	CAAGTCCGCA
10321	CCAGGTAAGT	GTATCCCAAC	AAAAAGTGCG	CGGGCGGCTG	CGGTCGAGG	GGCCAGCGTA
10381	GGGTGGCGGG	GGCTCCGGGG	CGGAGGTCTT	CCAACATAAG	CGGATGATAT	CCGTAGATGT
10441	ACCTGGACAT	CCAGGTGATG	CCGGCGGCGG	TGGTGGAGGC	CGCGGAAAG	TCAGCGACGC
10501	GGTTCCAGAT	GTTCGCGAGC	GGCAAAAAGT	GCTCCATGGT	CGGACGCTC	TGGCCGCTCA
10561	GGCGCGCGCA	GTCTTTGACG	CTCTAGACCG	TGCAAAAAGGA	GAGCTGTGTA	CGGGCGACTC
10621	TTCCGTGGTC	TGGTGGATAA	ATTGCAAGG	GTATCATGGC	GGACGACCGG	GGTTTCAACC
10681	CCGATCCCGG	CCGTCCGCGG	TGATCCATGC	GGTACCAGCC	CGCGTGTGCA	ACCCAGGTTG
10741	GCGAGTCCAG	ACAACGGGGG	AGCGCTCTCT	TTGGCTTCTT	TCAAGGCGCG	CGGATGCTGT

FIG. 11A-4

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10801 CGCTAGCTTT TTTGGCCACT GGCCGCGCGC GGCGTAAGCG GTTAGGCTGG AAAGCGAAAG  
 10861 CATTAAAGTGG CTCGCTCCCT GTAGCCGGAG GGTATTTTTC CAAGGGTTGA GTCGCGGGAC  
 10921 CCCCGGTTGC AGTCTCGGGC CGCCCGGACT CGCGCGAAGC GGGGTTTGCC TCCCGGTAC  
 10981 GCAAGACCCG GCTTGCAAAAT TCTCCGGAA ACAGGGACGA GCCCTTTTTC TGCTTTTCCC  
 11041 AGATGCATCC GGTGCTGCGG CAGATGCGCC CCCCCTCTCA GCAGCGGCAA GAGCAAGAGC  
 11101 AGCGGCAGAC ATGCAGGGCA CCTCTCCCTT CTCTACCGG GTCAGGAGGG GCAACATCCG  
 11161 CGGCTGACGC GGCGCCAGAT GGTGATTACG AACCCCGCGC GCGCCGAGG CGGCACTACT  
 11221 TGGACTTGGG GAGGGGCGAG GGCCTGGCGC GGCTAGGAGC GCCCTCTCCT GAGCGACACC  
 11281 CAAGGGTGCA GCTGAAGCGT GACACGCGCG AGGCGTACGT GCCGCGGAG AACCTGTTC  
 11341 GCGACCGGGA GGGAGAGGAG CCCGAGGAGA TCGCGGATCG AAAGTTCCAT GCAGGGCGCG  
 11401 AGTTGCGGCA TGGCCTGAAC CGCGAGCGGT TGCTGCGGGA GAGGAGACTT GAGCCCGAGC  
 11461 CGCGGACCGG GATTAGTCCC GCGCGCGCAC ACGTGGCGCG CGCCGACCTG GTAACCGGT  
 11521 ACGAGCAGAC GGTGAACCAG GAGATTAAC TTTAAAAAAG CTTTAAACAAC CAGCTGCACA  
 11581 CGCTTGTGGC GCGCGAGGAG GTGGCTATAG GACTGATGCA TCTGTGGGAG TTTGTAAGCG  
 11641 CGCTGGAGCA AAACCCAAT AGCAAGCGCG TCATGGCGCA GCTGTTCTCT ATAGTGCAGC  
 11701 ACAGCAGGGA CAACGAGGCA TTCAGGGATG CGCTGCTAAA CATAGTAGAG CCCGAGGGCC  
 11761 GCTGGCTGCT CAGTTTGATA AACATTCTGC AGAGCATAGT CAGTCTGGGC AAGTTTACG  
 11821 GCCTGGCTGA CAAGGTGGCC GCCATTAAC ATTCCATGCT CAGTCTGGGC AAGTTTACG  
 11881 CCCGCAAGAT ATACCATAAC CCTTACGTTT CCATAGACAA GGAGGTAAG ATCGAGGGGT  
 11941 TCTACATGCG CATGGCGCTG AAGGTGCTTA CTTGAGCGA CGACTCTGGG GCTTTATCGA  
 12001 ACGAGCGCAT CCACAAGGCC GTGAGCGTGA GCCGCGGGCG CGAGCTCAGC GACCGCGAGC  
 12061 TGATGCACAG CCTGCAAAAG GCCCTGGCTG GCACGGGCG CGGCGATGGA GAGGCCGAGT  
 12121 CCTACTTTGA CGCGGGCGCT GACCTGCGCT GGGCCCAAAG CCGACGCGCC CTGGAGGCAG  
 12181 CTGGGGCCGG ACCTGGGCTG CGCGTGGCAC CGCGCGCGCG TGGCAACGTC GGCGGCGTGG  
 12241 AGGAATATGA CGAGGACGAT GAGTACGAGC CAGAGGACGG CGAGTACTAA GCGGTGATGT  
 12301 TTCTGATCAG ATGATGCAAG ACGCAACGGA CCCGCGGGTG CGGCGGGCGC TGCAGAGCCA  
 12361 GCCGTCCGGC CTTAACTCCA CGGACGACTG CGGCCAGGTC ATGGAACGCA TCATGTGCTG  
 12421 GACTGCGCGC AACCTGACG CGTTCCGGCA GCAGCCGACG GCCAACCGGC TCTCCGCAAT  
 12481 TCTGGAAGCG GTGGTCCCAG CGCGCGCAAA CCCACGCGAC GAGAAGGTGTG TGGCGATGCT  
 12541 AAACGCGCTG GCGGAAAACA GGGCCATCCG GCCCGATGAG GCCGGCTGG TCTACGACGC  
 12601 GCTGCTTCAG CGCGTGGCTC GTTACAACAG CAGCAACGTC CAGACCAACC TGGACCGGCT  
 12661 GTGGGGGAT GTGCGCGAGG CCGTGCGCGA CGGTGAGCG CGCGCAGCAG AGGGCAACCT  
 12721 GGGCTCCATG GTTGCACTAA ACGCTTCTCT GAGTACACAG CCCGCCAACG TGGCGGGGG  
 12781 ACAGGAGGAC TACACCAACT TTGTAGGCGC ACTCGGCGTA ATGCTGACTG AGACACCGCA  
 12841 AAGTGAGGTG TATCAGTCCG GGCCAGACTA TTTTTCCTAG ACCAGTAGAG AAGGCTTGCA  
 12901 GACCGTAAAC CTGAGCAAGG CTTTCAAGAA CTTGCAAGGG CTGTGAGGGG CTGGGGCTCC  
 12961 CACAGGCGAC CGCGGACCGC TGTCTAGCTT GCTGACGCC AACTCGCGCC TGTTGTGCTG  
 13021 GCTAATAGCG CCTTACGCG ACAGTGGCAG CGTGTCCCGG GAGCATATGT GACGAGCATA CTTTCCAGGA  
 13081 GCTGACACTG TACCGCGAGG CCATAGGTCA GGCATGCTG GAGGAGCAGT GGCAGCTCTG AGGCAACCTC  
 13141 GATTACAAGT GTTAGCCGCG CGCTGGGGCA GGAGGACACG GGCAGCTCTG AGGCAACCTC  
 13201 GAACACTCTG CTGACCAACC GCGCGCAAAA AATCCCTCG TTAGCAGAGT TAAACAGCGA  
 13261 GAGGAGCGCG ATTTTGCCT ATGTGACGCA GAGCGTGAGC CTTAACCTGA TGCAGGACCG  
 13321 GGTAAACGCC AGCGTGGCG TGGACATGAG CGCGCGAAC ATGGAACCGG GCATGTATGC  
 13381 CTCAAACCGG CCGTTTATCA ATCGCTTAAT GGACTACTGT CATCGCGCG CGCGCGTGA  
 13441 CCCCAGATAT TTCACCAATG CCATCTTGAA CCGCAGACTG CTACCGCCCC CTGGTTTCTA

FIG. 11A-5

60/70

13501 CACCGGGGGA TTGAGGTTGC CCGAGGGTAA CGATGGATTG CTCTGGGACG ACATAGACGA  
 13561 CAGCGTGT TTCCCGCAAC CGCAGACCCT GCTAGAGTTG CAACAACGCG AGCAGGCAGA  
 13621 GGGCGCGCTG CGAAAGGAAA GCTTCCGCGAG GCCAAGCAGC TTGTCCGATC TAGGCGCTGC  
 13681 GGGCCCGCGG TCAGATGCTA GTAGGCCATT TCCAAGCTTG ATAGGCTCTC TTACGAGCAC  
 13741 TCGACCACC CGCCCGCGCC TGCTGGGCGA GGAGGAGTAC CTAACAACAT CGCTGCTGCA  
 13801 GCCGACGCG GAAAAAGAAC TGCTCCCGCG GTTTCCTCAAC AACGGGATAG AGAGCCTAGT  
 13861 GGACAAGATG AGTAGATGGA AGACGTATGC GCAGGAGCAC AGGGATGTGC CCGGCCCGCG  
 13921 CCCGCCACC CGTCGTCAAA GGCACGACCG TCACGCGGGT CTGGTGTGGG AGGACGATGA  
 13981 CTCGGCAGC GACAGCAGCG TCTTGGATTT GGGAGGGAGT GGCAACCCGT TTGCACACCT  
 14041 TGCCCCCAGG CTGGGGAGAA TGTTTTTAAAA AAAGCATGAT GCAAAATAAA AAACCTACCA  
 14101 AGGCCATGCG ACCGAGCGTT GGTTTTCTTG TATTTCCCTT AGTAGCGGCG GCGCGCGCAT  
 14161 GTATGAGGAA GGTCTCTCTC CCTCTACGA GAGCGTGGTG AGCGCGGCGC CAGTGGCGCG  
 14221 GGGCTGGGT TCACCTTCG ATGCTCCCTT GGACCCGCGG TTGTCGCTCT CGCGGTACCT  
 14281 GCGGCTTACC GGGGGGAGAA ACAGCATCCG TTACTCTGAG TTGGCACCC TATTGCACAC  
 14341 CACCGTGTGT TACCTTTGGT ACAACAAGTC AACGSGATGT GCATCCCTGA ACTACCAGAA  
 14401 CGACGACAGC AACTTTCTAA CCACGGTCAT TCAAAACAAT GACTACAGCC GCGGGGAGCG  
 14461 AAGCACACAG ACCATCAATC TTGACGACCG GTCCGACTGG AGCGCGGACC TGAAAACCAT  
 14521 CCTGCATACC AACATGCCAA ATGTGAACGA GTTCATGTTT ACCAATAAGT TTAAGCGCGT  
 14581 GGTGATGGTG TCGCGCTCGC TTAATGAAGA CAAACAGGTG GAGCTGAAT ACGAGTGGGT  
 14641 GGAGTTCACG CTGCCCGAGG GCAACTACTC CGAGACCATG ACCATAGACC TTATGAACAA  
 14701 CGCATCGTG GAGCACTACT TGAAGTGGG CAGGCAGAAC GGGGTTCTGG AAAGCGACAT  
 14761 CGGGGTAAAG TTTGACACCC GCAACTTCAG ACTGGGGTTT GACCCAGTCA CTGCTTTTGT  
 14821 CATGCCGGG GTATATACAA ACGAAGCCTT CCATCCAGAC ATCATTTTGC TGCCAGGATG  
 14881 CGGGGTGGAC TTACCCACCA GCGGCTGAG CAACTTGTG GGCATCCGCA AGCGGCAACC  
 14941 CTTCACGGAG GGCCTTTAGGA TCACCTACGA TGACCTGGAG GGTGGTAACA TTCCCGCACT  
 15001 GTTGATGTG GACGCCCTACC AGGCAAGCTT GAAAGATGAC ACCGAACAGG GCGGGGGTGG  
 15061 CGCAGGCGCG GGCAACAACA GTGGCAGCGG CGCGGAAGAG AACTCCAACG CGGACGCTGC  
 15121 GGCAATGCAG CCGGTGGAGG ACATGAACGA TCATGCCATT CGCGGCGACA CTTTGGCCAC  
 15181 ACGGGCGGAG GAGAAGCGCG CTGAGGCCGA GGCAGCGGCG GAAGCTGCGC CCCCCTGTC  
 15241 GGAGGCTGCA CAACCCGAGG TCGAGAAGCC TCAGAAGAAA CCGGTGATTA AACCCCTGAC  
 15301 AGAGGACAGC AAGAAACGCA GTTACAACCT AATAAGCAAT GACAGCACTC TCACCCAGTA  
 15361 CGCAGCTG TGCTTTGCAT ACAACTACGG CGACCTTCAG GCCGGGATCC GCTCATGGAG  
 15421 CTGCTTTTGC ACTCTGACG TAACCTGCGG CTCGGAGCAG GTATATCTGGT CTTTGGCCGA  
 15481 CATGATGCAA GACCCGCTGA CCTTCCGCTC CACGCGCCAG ATCAGCAACT TTCCGGTGGT  
 15541 GGGCGCCGAG CTGTTGCCCG TGCACTCCAA GAGCTTCTAC AACGACGAGG CCGCTACTAC  
 15601 CCAGCTCATC CGCCAGTTTA CCTCTGTGAC CCACGTGTTT AATCGCTTTC CCGAGAACCA  
 15661 GATTTTGGCG CGCCCGCCAG CCCCACCAAT CACCAACGTC AGTGAAACG TTCTGTCTCT  
 15721 CACAGTCAC GGGACGCTAC CGCTGCGCAA CGCATCGGA GGAGTGGTGG AGAGGCGCG  
 15781 TACTGACGCC AGACGCCGCA CCTGCCCTTA CGTTTACAG GCGCTGGGCA TAGTCTGCC  
 15841 GCGGCTCCTA TCGAGCCGCA CTTTGTGAG AAGCATGTCC ATCCTTATAT CGCCAGCAA  
 15901 TAACACAGG GGGGCTGCG GCTTCCCAAG CAAGATGTTT GCGGGGGCCA AGAAGCGCTC  
 15961 CGACCAACAC CCACTGCGCG TGCGGGGCA CTACCGCGCG CCCTGGGGCG CGCACAACG  
 16021 CGGCGCATC GGGCGCACCA CGCTGATGTA GCGCATGCAC CGGTTGGTGG AGAGGCGCG  
 16081 CAAC TACACG CCCACGCCGC CGCCAGTGTC CACCTGSGAC GCGGCCATTC AGACCGTGGT  
 16141 GCGCGGAGCC CCGGCGTACG CTAATATGAA GAGACGGCGG AGGCGCGTAG CACGTGCCA

FIG. 11A-6

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16201 CCGCCGCGGA CCCGGCACTG CCGCCCAACG CCGCGCGGCG GCCCTGCTTA ACCGCGCACG  
 16261 TCGCACCGCG CGACGGGCGG CCATGCGAGC CGCTCGAAGG CTGGCGCGGG GTATTGTTCAC  
 16321 TGTGCCCCCC AGGTCCAGGC GACGAGCGCG CGCCGCGACA GCCGCGGCCA TTAGTGCTAT  
 16381 GACTCAGGGT CGCAGGGGCA ACGTGTACTG GGTGCGCGAC TCGGTTAGCG GCCTGCGCGT  
 16441 GCCCGTGCGC ACCCGCCCCC CGCGCAACTA GATTGCAATA AAAAATCAT TACATCGTA  
 16501 CTGTTGTATG TATCCAGCGG CGCGCGCGCG CATCGAAGCT ATGTCCAAGC GCAAAATCAA  
 16561 AGAAGAGATG CTCCAGGTCA TCGCGCCGGA GATCTATGGC CCCCCGAAGA AGGAAGAGCA  
 16621 GGATTACAAG CCCCCAAAGC TAAAGCGGGT CAAAAAGAAA AAGAAAGATG ATGATGATGA  
 16681 TGAACCTTGAC GACGAGGTGG AACTGTTGCA CGCGACCGCG CCCAGGCGAC GGGTACAGTG  
 16741 GAAAGGTGCA CGCGTAAGAC GTGTTTTGCG ACCCGGCACC ACCGTAGTCT TTACGCCCGG  
 16801 TGAGCGCTCC ACCCGCACCT ACAAGCGCGT GTATGATGAG GTGTACGGCG ACGAGGACCT  
 16861 GCTTGAGCAG GCCAACGAGC GCCTCGGGGA GTTTGCCTAC GGAAAGCGGC ATAAAGGCAT  
 16921 GCTGGCGTTG CCGCTGGACG AGGGCAACCC AACACCTAGC CTAAGGCCCG TGACACTGCA  
 16981 CGAGGTGCTG CCGCGGCTTG CACCGTCCGA AGAAAGCGC GGCCTAAAGC GCGAGTCTGG  
 17041 TGACTTGGCA CCCACCGTGC AGCTGATGGT ACCCAAGCGT CAGCGACTGG AAGATGTCTT  
 17101 GGAAAHATHT ACCGTGGAGC CTGGGCTGGA GCCCGAGGTG CGCGTGCGGC CAATCAAGCA  
 17161 GGTGGCACCG GCACTGGGCG TGCAGACCGT GGACGTTGAG ATACCCACCA CAGTAGCAC  
 17221 TAGTATTGCC ACTGCCACAG AGGGCATGGA GACACAAAGC TCCCCGGTGG CCTCGGCGGT  
 17281 GGCAGATGCC GCGGTGACGG CCGCGCTGCG GGC CGCGTCC AAGACCTCTA CGGAGGTGCA  
 17341 AACCGACCCG TGGATGTTTC GTGTTTCAGC CCGCGCGCGT CCGCGCGGTG CAGGAAGTA  
 17401 CGCGCGCGCC AGCGCGTAC TGCCCGAATA TGCCCTACAT CCTTCCATCG CGCCTACCCC  
 17461 CGGCTATCGT GGGTACACCT ACCGCCACAG AAGCAGAGCA ACTACCCGAC GCCGAACCC  
 17521 CACTGGAACC CGCGCGCGCC GTCCGCGTGG CAGGCCCGTG GTGGCCCCGA TTTCCGTGCG  
 17581 CAGGGTGGCT CGCGAAGGAG GCAGGACCCT GGTGCTGCGA ACAGCGCGCT ACCACCCAG  
 17641 CATCGTTTAA AAGCCGGTCT TTGTGGTTCT TGCAGATATG GCCCTACCT GCGCGCTCCG  
 17701 TTTCCCGGTG CCGGGATTCC GAGGAAGAAT GCACCGTAGG AGGGGCATGG CGGCCACCG  
 17761 CCGTACGGGG GGCATGCGTC GTGCGCACCA CCGCGCGCGG CGCGCGTCGC ACCGTGCGAT  
 17821 GCGCGCGGGT ATCTCGCCC TCCTTATTCC ACTGATCGCC CGCGCGATTG GCGCGGTGCC  
 17881 CGGAATTGCA TCCGTGGCCT TGCAGGCGCA GAGACACTGA TTAATAACAA GTTACATGTG  
 17941 GAAAAATCAA AATAAAGTC TGGACTCTCA CGCTCGCTTG GTCTCTGAAC TATTTTGTAG  
 18001 AATGGAAGAC ATCAACTTTG CGTCACTGGC CCGCGGACAC GGCCTGCGCC CGTTCATGGG  
 18061 AAATGGCAA GATATCGGCA CCAGCAATAT GAGCGGTGGC GCCTTCAGCT GGGGCTCGCT  
 18121 GTGGAGCGGG ATTAATAATT TCGGTTCCGC CGTTAAGAAC TATGGCAGCA AAGCCTGGAA  
 18181 CAGCAGCACA GGCCAGATGC TGAGGGACAA GTTGAAGAG CAAAATTTCC ACAAAAAGGT  
 18241 GGTGATAGGC CTGGCTCTG GCATTAGCGG GGTGGTGGAC CTGGCCACAC CAGGAGGTGCA  
 18301 AATAAAGATT AACAGTAAGC TTGATCCCGC CCTCCCGTA GAGGAGCCTC CACCGGCGGT  
 18361 GGAGACAGTG TCTCCAGAGG GCGGTGGCGA AAAGCGTCCG CGACCCGACA GGGGAAGAAC  
 18421 TCTGGTGACG CAAATAGACG AGCCTCCCTC GTACGAGGAG GCACATAAGC AAGGCTTGCC  
 18481 CACCACCGGT CCAATCGCGC CCATGGCTAC CGGAGTGGTG GGGCAGCACA CACCGTATAC  
 18541 GCTGGACCTG CCTCCCCCGG CCGACACCCA GCAGAAACCT GTGCTGCCAG GCCCGTCCG  
 18601 CGTGTGTTGA ACCGTCCTTA GCGCGCGTGC CCGCGCGGCG CCGCGGAGTC CCGCGGATC  
 18661 GTTGCGGGCC GTAGCCAGTG GCAACTGGCA AAGCACACTG AACAGCATCG TGGGTTTGGG  
 18721 GGTGCAATTC CTGAAGCGCC GACGATGCTT CTGATAGCTA ACGTGTGCTGA TGTGTGTCAT  
 18781 GTATGCTGCC ATGTGCGCGC CAGAGGAGCT GCTGAGCGCG CCGCGCGCGG CTTTCCAAAG  
 18841 TGGCTACCCC TTGATGATG CCGCAGTGGT CTTACATGCA CATCTCGGGC CAGGACGCTT

FIG. 11A-7

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18901	CGGAGTACCT	GAGCCCCGGG	CTGGTGCAGT	TCGCCCGCGC	CACCGAGACG	TACTTCAGCC
18961	TGAATAACAA	GTTTAGAAAC	CCCACGGTGG	CGCCTACGCA	CGACGTGACC	ACAGACCCGGT
19021	CTCAGCGTTT	GACGCTCGGG	TTATCCCGCG	TGGACCCGGA	GGATACTCGG	TACTCGTACA
19081	AGGCGCGGTT	ACCCTAGCTG	GTGGGTGATA	ACCGTGTGCT	AGACATGGCT	TCCACGTACT
19141	TTGACATCCG	CGGCGTGTGT	GACAGGGGCC	CTACTTTTAA	GCCCTACTCT	GGCACTGCCT
19201	ACAACGCACT	GGCCCCCAAG	GGTGCCCCCA	ACTCGTGCGA	GTGGGAACAA	AATGAACTGT
19261	CACAAGTGGG	TGCTCAAGAA	CTTGACGAAG	AGGAGAATGA	AGCCAATGAA	GCTCAGGCGC
19321	GAGAACAGGA	ACAAGCTAAG	AAAACCCATG	TATATGCCCA	GGCTCCACTG	TCCGGAATAA
19381	AAATAACTAA	AGAAGGTCTA	CAAAATAGGA	CTGCCGACGC	CACAGTAGCA	GGTGCCGGCA
19441	AAGAAATTTT	CGCAGACAAA	ACTTTTCAAC	CTGAACCACA	AGTAGGAGAA	TCTCAATGGA
19501	ACGAAGCGGA	TGCCACAGCA	GCTGGTGGAA	GGGTCTTTAA	AAAGACAAC	CCCATGAAC
19561	CCTGCTATGG	CTCATACGCT	AGACCCACCA	ATTCCAACGG	CGGACAGGGC	GTTATGGTTG
19621	AACAAAATGG	TAAATTGGAA	AGTCAAGTCG	AAATGCAATT	TTTTTCCACA	TCCACAAATG
19681	CCACAAATGA	AGTTAAACAT	ATACAACCAC	CAGTTGTATT	GTACAGCGAA	GATGTAAACA
19741	TGGAACACTC	AGATACTCAT	CTTTCTTATA	AACTTAAAT	GGGGGATAAA	AATGCCAAAG
19801	TCATGCTTGG	CAACAAGCA	ATGCCAAACA	GACCAAAATTA	CATTGCTTTT	AGAGACAATT
19861	TTATTGGTCT	CATGTATTAC	AACAGCACAG	GTAACATGGG	TGCTCTTGCT	GGTCAGGCAT
19921	CGCAGTTGAA	CGCTGTTGTA	GATTTGCAAG	ACAGAAACAC	AGAGCTGTCC	TACCAGCTTT
19981	TGCTTGATTC	AATTGGCGAC	AGAACAAGAT	ACTTTTCAAT	GTGGAAATCA	GCTGTTGACA
20041	GCTATGATCC	AGATGTACGA	ATTATTGAGA	ACCATGGAAC	TGAGGATGAG	TTGCCAAATT
20101	ATTGCTTTCC	TCTTGGTGGA	ATTGGGATTA	CTGACACTTT	TCAAGCTGTT	AAAACAACGT
20161	CTGCTAACGG	GGACCAAGGC	AATACTACCT	GGCAAAAAGA	TTCAACATT	GCAGAACGCA
20221	ATGAAATAGG	GGTGGGAAAT	AACTTTGCCA	TGGAATTA	CCTGAATGCC	AACTATGGA
20281	GAAATTTTCT	TTACTCCAAT	ATTGCGCTGT	ACCTGCCAGA	CAAGCTAAAA	TACAACCCCA
20341	CCAAGTGGA	AATATCTGAC	AACCCCAACA	CCTACGACTA	CATGAACAAG	CGAGTGGTGG
20401	CTCCTGGGCT	TGTAGACTGC	TACATTAAAC	TGGGGGCGCG	CTGGTCTCTG	GACTACATGG
20461	ACAACGTTAA	TCCCTTTAAC	CACCACCGCA	ATGCGGGCCT	CGGTTACCGC	TCCATGTTGT
20521	TGGGAAACGG	CCGCTACGTG	CCCTTTCACA	TTCAAGTGCC	CCAAAAGTTT	TTTGCCATT
20581	AAAACCTCCT	CCTCCTGCCA	GGCTCATACA	CATATGAATG	GAACCTTCAG	AAGGATGTTA
20641	ACATGGTTCT	GCAGAGCTCT	CTGGGAAACG	ACCTTAGAGT	TGACGGGGCT	AGCATTAAAT
20701	TTGACAGCAT	TTGTCTTTAC	GCCACCTTCT	TCCCATGGC	CCACAACAGC	GCCTCCACG
20761	TGGAAGCCAT	GCTCAGAAAT	GACACCAACG	ACCAGTCCCT	TAATGACTAC	CTTTCCCGCG
20821	CCAACATGCT	ATATCCCAT	CCGCGCAACG	CCACCAAGCT	GCCCTCTCC	ATCCCATCGC
20881	GCAACTGGGC	AGCATTTGCG	GGTTGGGCCT	TCACACGCTT	GAAGACAAG	GAACCCCTT
20941	CCCTGGGATC	AGGCTACGAC	CCTTACTACA	CTACTCTGG	CTCATACCA	CTCTTGAGC
21001	GAACCTTCTA	TCTTAATCAC	ACCTTTAAGA	AGGTGGCCAT	TACTTTTGAC	TCTTCTGTTA
21061	GCTGGCCGGG	CAACGACCGC	CTGCTTACTC	CCAATGAGTT	TGAGATTAA	CGCTCAGTTG
21121	ACGGGGAGGG	CTATAACGTA	GCTCAGTGCA	ACATGACAAA	GGACTGGTCT	CTAGTCAGCA
21181	TGTTGGCCAA	CTACAATATT	GGCTACCAAG	GCTTCTACAT	TCCAGAAAGC	TACAAAGACT
21241	GCATGTACTC	GTTCCTCAGA	AACTTCCAGC	CCATGAGCCG	GCAAGTGGTG	GACGACTACT
21301	AATACAAAGA	TTATACGACG	GTGGGAATTA	TCCACCAGCA	TAACAACCTA	GGCTTCGTAG
21361	GCTACCTCGC	TCCACCATGT	CGCGAGGGAC	AAGCTTACCC	CGCTAATGTT	CCCTACCCAC
21421	TAATAGGCAA	AACCGCGGTT	GATAGTATTA	CCGAGAAAAA	GTTCCTTTGC	GACCTGACCC
21481	TGTGGCGCAT	CCCTTCTTCC	AGTAACTTTA	TGTCATGGG	TGCGCTCACA	GACCTGGGCC
21541	AAAACCTTCT	CTACGCAAAC	TCCGCCACGC	CGCTAGACAT	GACCTTTGAG	GTGGATCCCA

FIG. 11A-8

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21601 TGGACGAGCC CACCCTTCTT TATGTTTGT TTGAAGTCTT TGACGTGGTC CGTGTGCACC  
 21661 AGCCGCACCG CGCGTTCATC GAGACCGTGT ACCTGCGCAC GCCCTTCTCG GCCGGCAACG  
 21721 CCACACACATA AAGAAGCAAG CAACATCAAC AACAGCTGCC GCCATGGGCT CCAGTGAGCA  
 21781 GGAAGTGAAA GC.CATTGTCA AAGATCTTGG TTGTGGGGCA TATTTTTTGG GCACCTATGA  
 21841 CAAGCGCTTC CCAGGCTTTG TTTCCCCACA CAAGCTCGCC TGGCCCATAG TTAACACGGC  
 21901 CGGTGCGCAG ACTGGGGGCG TACACTGGAT GGCTTTTGCC TGGAAACCGC GCTCAAAAAC  
 21961 ATGCTACCTC TTTGAGCCCT TTGGCTTTTC TGACCAACGT CTCAAGCAGG TTACACAGTT  
 22021 TGAGTACGAG TCACTCCTGC GCGGTAGCGC CATTGCCTCT TCCCCGACCC GCTGTATAAC  
 22081 GCTGAAAAAG TCCACCCAAA GCGTGCAGGG GCCCAACTCG GCCGCTGTG GCTATTCTCG  
 22141 CTGCATGTTT TCCACGCGCT TTGCCAACTG GCCCAAACT CCCATGGATC ACAACCCAC  
 22201 CATGAACCTT ATTACCGGGG TACCCAACTC CATGCTTAAC AGTCCCCAGG TACAGCCAC  
 22261 CCTGCGCCCG AACCAGGAAC AGCTCTACAG CTTCTGGAG CGCCACTCGC CCTACTTCG  
 22321 CAGCCACAGT GCGCAAATTA GAGAGGCCAC TTCTTTTGT CACTTGAAAA ACATGTAAAA  
 22381 ATAATGTACT AGGAGACACT TTCAATAAAG GCAAATGTTT TTATTTGTAT ACTCTCGGGT  
 22441 GATTATTTAC CCCACCCCTT GCGCTCTGCG CCGTTTAAAA ATCAAAGGGG TTCTGCCGCG  
 22501 CATCGCTATG CGCCACTGGC AGGGACACGT TCGCATACTG GTGTTTTAGTG CTCACCTTAA  
 22561 ACTCAGGCAC AACCATCCGCG GGCAGCTCGG TGAAGTTTTC ACTCCACAGG TCGCCACCA  
 22621 TCACCAACGC GTTTAGCAGG TCGGGCGCGC ATATCTTGAA GTGCGAGTTG GGGCTCCCG  
 22681 CCTGCGCGCG CGAGTTGCGA TACACAGGGT TACAGCACTG GAACACTATC AGCGCCGGGT  
 22741 GGTGCACGCT GCCCAGCACG CTCTTTGTCG AGATCAGATC CGCGTCCAGG TCTCCCGGT  
 22801 TGCTCAGGGC GAACGAGTC AACTTTGTTG GCTGCCCTCC CAAAAAGGGT GCATGCCAG  
 22861 GCTTTGAGTT GCACTCGCAC CGTAGTGGCA TCAGAAGGTG ACCGTGCCCA GCTCTGGCGT  
 22921 TAGGATACAG CGCTGTCATG AAAGCCTTGA TCTGCTTAAA AGCCACCTGA GCCTTTGCGC  
 22981 CTTACAGAAA GAACATGCCG CAAGACTTGC CGGAAAACTG ATTGCCCGGA CAGGCCCGGT  
 23041 CATGCACGCA GCACCTTGCG TCGGTGTGG AGATCTGCAC CACATTTGCG CCCCACCGGT  
 23101 TCTTACGAT CTGGGCTTG CTAGACTGCT CTTTACGCGC GCGCTGCCCG TTTTCGCTCG  
 23161 TCACATCCAT TTCAATCACG TGCTCTTAT TTATCATAAT GCTCCCGTGT AGACACTTAA  
 23221 GCTGCCCTTC GATCTCAGCG CAGCGGTGCA GCCACAACGC GCAGCCCGTG GGTCTGTGTT  
 23281 GCTTGATAGT TACCTCTGCA AACGACTGCA GGTACGCGTG CAGGAATCGC CCATCATGCG  
 23341 TCACAAAGGT CTGTTGCTG GTGAAGGTCA GCTGCAACGC GCGGTGCTCC TCGTTTAGCC  
 23401 AGGTCTTGCA TACGGCGGCC AGAGCTTCCA CTGGGTGAGG CAGTAGCTTG AAGTTTGCTT  
 23461 TTAGATCGTT ATCCACGTGG TACTTGTCCA TCAACGCGCG CGCAGCTTCC ATGCCCTTCT  
 23521 CCCACGCAGA CACGATCGGC AGGCTCAGCG GGTATTATCAC CGTGTCTTCA CTTTCCGCTT  
 23581 CACTGGACTC TTTCTTTTCC TCTTGCATCC GCATACCCCG CGCCACTGGG TCGCTTCATC  
 23641 TCAGCCGCGC CACCGTGCAG TTACTCTCCT TGCCGTGCTT GATTAGCACC GGTGGGTTGC  
 23701 TGAACCCAC CATTTGTAGC GCCACATCTT CTCTTTCTTC CTCGCTGTCC ACACATCCTT  
 23761 CTGGGATAGG CGGGGCTCG GGTCTGGGAG AGGGGCGCTT CTTTTTCTTT TTGGACGCAA  
 23881 TGCCCAAATC CGCGCTCGAG GTCGATGGCC GCGGGCTGGG TGTCGCGCGC ACCAGCGCAT  
 23941 CTTGTGACGA GTCTTCTTCC TCCTCGGACT CGAGACGCGC CCTCAGCCGC TTTTTTGGGG  
 23941 GCGCGCGGGG AGGCGCGGCG GACGGCGAGC GGGACGAGAC GTCCCTCATG GTTGTGAGC  
 24001 GTGCGCGCGC ACCGCTCCG CGCTCGGGGG TGTTTTCGCG CTGCTCTCTT TCCGACTTGG  
 24061 CATTTCCTTT CTCCTATAGG CAGAAAAAGA TCATGGAGTC AGTCGAGAAG GAGGACAGCC  
 24121 TAACCGCCCC CTTTGAGTTC GCCACCCAG CCTCACCGA TGCGCCCAAC GCGCTTACCA  
 24181 CTTTCCCCGT CAGGACACCC CCGCTTGAGG AGGAGGAAGT GATTATCGAG CAGGACCCAG  
 24241 GTTTTGTAAAG CGAAGACGAC GAAGATCGCT CAGTACCAAC AGAGGATAAA AAGCAAGACC

FIG. 11A-9

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24301	AGGACGACGC	AGAGGCAAAAC	GAGGAACAAG	TCGGGCGGGG	GGACCAAAAG	CATGGCGACT
24361	ACCTAGATGT	GGGAGACGAC	GTGCTGTGTA	AGCATCTGCA	GCGCCAGTGC	GCCATTATCT
24421	CGCAGCGGCT	GCAAGAGCGC	AGCGATGTGC	CCCTCGCCAT	AGCGGATGTC	AGCCTTGCCCT
24481	ACGAACGCCA	CTGTGTTCTCA	CCGCGCGTAC	CCCCAAACG	CCAAGAAAAAC	GGCACAATGCG
24541	AGCCCAACCC	CGCGCTCAAC	TTCTACCCCG	TATTTGCCGT	GCCAGAGGTG	CTTCCGACCT
24601	ATCACATCTT	TTTCCAAAAC	TGCAAGATAC	CCCTATCCGT	CCGTGCCAAC	CGCAGCCGAG
24661	CGGACAAGCA	GCTGGCCTTG	CGCGAGGGCG	CTGTATACCC	TGATATCGCC	TCGCTCGACG
24721	AAGTGCCAAA	AATCTTTGAG	GGTCTTGGAC	CGCAGCGAAG	CGCGCGCGCA	AACGCTCTGC
24781	AACAAGAAAA	CAGCGAAAT	GAAAGTCACT	GTGGAGTGCT	GGTGGAACCT	GAGGGTGACA
24841	ACGCGCGCCT	AGCCGTGCTG	AAACGCAGCA	TCGAGGTAC	CCACTTTGCC	TACCCGCGAC
24901	TTAACTTACC	CCCCAAGGTT	ATGAGCACAG	TCATGAGCGA	GCTGATCGTG	CGCCGTGCAC
24961	GACCCCTGGA	GAGGGATGCA	AACTTGCAAG	AACAACCCGA	GGAGGGCCTA	CCCGCAGTTG
25021	GCATGAGCA	GCTGGCGCGC	TGGCTTGAGA	CGCGCAGGCC	TGCCGACTTG	GAGGAGCGAC
25081	GCAAGCTAAT	GATGGCCGCA	GTGCTTGTTA	CCGTGGAGCT	TGAGTGCATG	CAGCGGTTCT
25141	TTGCTGACCC	GGAGATGCAG	CGCAAGCTAG	AGGAAACGTT	GCACATACCC	TTTCGCCAGG
25201	GCTAGCTGGC	CCAGGCCGTG	AAAATTTCCA	ACGTGGAGCT	CTGCAACCTG	GTCTCCTTACT
25261	TTGGAAATTT	GCACGAAAAAC	CGCCTTGGGC	AAAACGTGCT	TCATTCCACG	CTCAAGGGCG
25321	AGGCGCGCGC	CGACTACGTC	CGCGACTGCG	TTTACTTATT	TCTGTGCTAC	ACCTGGCAAA
25381	CGGCCATGGG	CGTGTGGCAG	CAGTGCCGTG	AGGAGCGCAA	CCTGAAGGAG	GTGCAAGAAG
25441	TGCTAAAGCA	AAACTTTGAAG	GACCTATGGA	CGGCCTTCAA	CGAGCGCTCC	GTGGCCGCGC
25501	ACCTGGCGGA	CATTATCTTC	CCCGAACGCC	TGCTTAAAAC	CCTGCAACAG	GGTCTGGCAG
25561	ACTTCACCAG	TCAAAGCATG	TTGCAAAACT	TTAGGAACCT	TATCCTAGAG	CGTTCAGGAA
25621	TTCTGCCCGC	CACCTGCTGT	GCCTTCTCTA	CGGACTTTGT	GCCCAATTAAG	TACCGTGAAT
25681	GCCTCCGCC	GCTTTGGGGT	CACTGCTACC	TTCTGCAGCT	AGCCAACTAC	CTTGCTTACC
25741	ACTCCGACAT	CATGGAAGAC	GTGAGCGGTG	ACGGCCTACT	GGAGTGTAC	TGTCGCTGCA
25801	ACCTATGCAC	CCCGCACC	TCCTTGGTCT	GCAATTCACA	ACTGCTTAGC	GAAAGTCAAA
25861	TTATCGGTAC	CTTTGAGCTG	CAGGGTCCCT	CGCCTGACGA	AAAGTCCCGC	GCTCCGGGCT
25921	TGAAACTCAC	TCGGGGCTG	TGAGCTGCG	CTTACCTTCG	CAAAATTTGTA	CCTGAGGACT
25981	ACCACGCCCA	CGAGATTAGG	TTCTACGAAG	ACCAATCCCG	CCCGCCAAT	CGGAGCTTAA
26041	CGCGCTGCTG	CAITACCCAG	GGCCACATCC	TTGGCCAAAT	GCAAGCCATT	AACCAAGCCC
26101	GCCAAGAGTT	TCTGCTACGA	AAGGGACGGG	GGGTTTACTT	GGACCCCCAG	TCCGCGCAGG
26161	AGCTCAACCC	AATCCCCCGC	CCGCGCAGC	CCTATCAGCA	GCCGCGGGCC	CTTGCTTCCC
26221	AGGATGGCAC	CCAAAAGAA	GCTGCAGCTG	CCGCGCCGCG	CACCCACGGA	CGAGGAGGAA
26281	TACTGGGACA	GTACGGCAGA	GGAGGTTTTG	GACGAGGAGG	AGGAGATGAT	GGAGAGCTGG
26341	GACAGCCTAG	ACGAGGAAGC	TTCCGAGGCC	GAAGAGGTGT	CAGACAAAC	ACCGTACCCC
26401	TCGGTCCGAT	TCCCTTCGCC	GGCGCCCAAG	AAATCGGCAA	CCGTTCCAG	CATTGCTACA
26461	ACCTCCGCTC	CTCAGGCGCC	GCCGCGACTG	CCCGTTCCGC	GACCAACCG	TAGATGGGAG
26521	ACCACCTGAA	CAGGGGCCGG	TAACTTAAG	CAGCGCCGCG	CGTTAGCCCA	AGAGCAACAA
26581	CAGCGCCAA	GCTACCGCTC	GTGGCGCGTG	CACAAGAACG	CCATAGTTGC	TGCTTTGCAA
26641	GACTGTGGGG	GCAACATCTC	CTTCGCCCGC	CGCTTTCTTC	TCTACCATCA	CGCGCTGGCC
26701	TTCCCCCGAT	CATCTCTGCA	TTACTACCGT	CATCTCTACA	GCCTTACTTG	CACCGCGGCG
26761	AGCGGCGACA	ACAGCAGCGG	CCACGACGAA	GCAAGGCGGA	CCGGATAGCA	AGACTCTGAC
26821	AAAGCCCAAG	AAATCCACAG	CGCGGGCAGC	AGCAGGAGGA	GGAGCACTCG	GCTTGGCGCC
26881	CAACGAACCC	GTATCGACCC	CGGAGCTTAG	AAACAGGATT	TTTCCCACTC	TGATATGCTAT
26941	ATTTCAACAG	AGCAGGGGCC	AAGAACAAGA	GCTGAAATAA	AAAAACAGGT	CTCTGCGCTC

FIG.11A-10

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27001 CCTCACCCGC AGCTGCCTGT ATCACAAAAG CGAAGATCAG CTTGCGGCGA CGCTGGAAGA  
 27061 CGCGGAGGCT CTCTTCAGCA AATACTGCGC GCTGACTCTT AAGGACTAGT TTCGCGCCCT  
 27121 TTCTCAAAAT TAAGCGCGAA AACTACGTCA TCTCCAGCGG CCACACCCGG CGCCAGCACC  
 27181 TGTGCTCAGC GCCATTATGA GCAAGGAAAT TCCACGCCCC TACATGTGGA GTTACCAGCT  
 27241 ACAAATGGGA CTTGCGGCTG GAGCTGCCCA AGACTACTCA ACCCGAATAA ACTACATGAG  
 27301 CGCGGAGACC CACATGATAT CCCGGGTCAA CGGAATCCGC GCCCACCGBA ACCGAATTCT  
 27361 CCTCGAACAG GCGGCTATTA CCACCACACC TCGTAATAAC CTTAATCCCC GTAGTTGGCC  
 27421 CGCTGCCCTG GTGTACCAGG AAAGTCCCGC TCCACCACCT GTGGTACTTC CCAGAGACGC  
 27481 CCAGGCCGAA GTTCAGATGA CTAAGTCAGG GCGCAGCTT GCGGGCGGCT TTCGTCACAG  
 27541 GGTGCGGTG CCGGCGCAGG GTATAACTCA CCTGAAAATC AGAGGGCGAG GTATTAGCT  
 27601 CAACGACGAG TCGGTGAGCT CCTCTCTGG TCTCGTCCG GACGGGACAT TTCAGATCGG  
 27661 CGGCGCTGGC CGCTCTTCAT TTACGCCCGC TCAGGCGATC CTAAGCTGCG AGACCTCGTC  
 27721 CTCGAGCCGG CGCTCCGGAG GCATTGGAAC TCTACAATTT ATTGAGGAGT TCGTGCCCTC  
 27781 GGTTTACTTC AACCCCTTTT CTGGACCTCC CGGCCACTAC CCGGACAGT TTAITCCCAA  
 27841 CTTTGACGCG GTAAAAGACT CGCGGACGCG CTACGACTGA ATGACCAAGT GAGAGGCAGA  
 27901 GCAACTCGCC CTGACACACC TCGACCACCT CGCGGCCAC AAGTGTCTTG CCCGCGCTC  
 27961 CGGTGAGTTT TGTTACTTTG AATTGCCCGA AGAGCATATC GAGGGCCCGG CGCAGCGGCT  
 28021 CGGGCTCACC ACCCAGGTAG AGCTTACACG TAGCCTGATT CGGGAGTTTA CCAAGCGCCC  
 28081 CCTGCTAGTG GAGCGGGAGC GGGGTCCCTG TGTTCTGACC GTGGTTTGCA ACTGTCTTAA  
 28141 CCTCGGATTA CATCAAGATC TTTGTTGTCA TCTCTGTGCT GAGTATAATA AATACAGAAA  
 28201 TTAGAATCTA CTGGGGCTCC GTGCGCCATC CTGTGAACGC CACCGTTTTT ACCCACCAAA  
 28261 AGCAGACCAA AGCAAACTCT ACCTCCGGTT TGCACAAGCG GGCCAATAAG TACCTTACCT  
 28321 GGTACTTTAA CGGCTCTTCA TTTGTAATTT ACAACAGTTT CCAGCGAGAC GAAGTAAGTT  
 28381 TGCCACACAA CCTTCTCGGC TTCAACTACA CCGTCAAGAA AAACACCACC ACCACCTTCC  
 28441 TCACCTGCGG GGAACGTACG AGTGCGTCAC CGGTTGCTGC GCCCACACCT ACAGCCTGAG  
 28501 CGTAACCAGA CATTACTCCC ATTTTCCCAA AACAGGAGGT GAGCTCAACT CCGCGAACTC  
 28561 AGGTCAAAAA AGCATTTTGC GGGGTGCTGG GATTTTTTAA TTAAGTATAT GAGCAATTCA  
 28621 AGTAACCTCA CAAGCTTGTG TAATTTTCTT GGAATTGGGG TCGGGGTTAT CTTTACTCTT  
 28681 GTAATTCTGT TTATTCTTAT ACTAGCATT CTGTGCTTAA GGGTTGCCCG CTGCTGCACG  
 28741 CACGTTTTGA CCTATTGTCA GCTTTTTAAA CGCTGGGGGC GACATCCAAG ATGAGGTACA  
 28801 TGATTTTAGG CTTGCTCGCC CTTGCGGCG TCTGCAAGCG TGCCAAAAAG GTTGAGTTTA  
 28861 AGGAACCAAG TTGCAATGTT ACATTTAAT CAGAAGCTAA TGAATGCAC ACTCTTATAA  
 28921 AATGCACCAC AGAACATGAA AAGCTTATTA TTGCGCCAAA AGACAAAAAT GGCAGATATG  
 28981 CTGTATATGC TATTGCGCAG CCAGGTGACA CTAACGACTA TAATGTGACA GTCTTCCAAAG  
 29041 GTGAAAAATG TAAACTTTTT ATGTATAAAT TTCCATTTTA TGAATTTGCA GATAATTACA  
 29101 TGTACATGAG CAACAGTAC AAGTTGTGG CCCCACAAAA GTGTTTAGAG AACACTGGCA  
 29161 CCTTTGTTTC CACCGCTCTG CTTATTACAG CGCTTGCTTT GGTATGTACC TTACTTTATC  
 29221 TCAAAATCAA AAGCAGACGC AGTTTTATTG ATGAAAAGAA AATCGCTTGA TTTCGCTTTC  
 29281 GCTTGTATTG CCTTGGACAA TTACTCTTAT GTGGGATATG CGCCAGCGGG GAAAGATTAT  
 29341 ACCCACAACC TTCAAAATCAA ACTTCTCTGG ACGTTAGCGC CTGACTTCTG CCAGCGCCTG  
 29401 CACTGCAAAAT TTGATCAAAC CCAGCTTACG CTTGCGCTCG CCAGAGATGA CCGGCTCAAC  
 29461 CATCGCGCCC ACAACGGACT ATCGCAACAC CACTGCTACC GGACTAAAAAT CTGCCCTAAA  
 29521 TTTACCCCAA GTTCATGGCT TTGTCAAATG CTGGGCGAGC TTGGGCTATG GGTGCTTTTC  
 29581 CATAGCGCTT ATGTTTGTGT GCCTTAITAT TATGTGGCTT ATTTGTTGCC TAAAGCGCAG  
 29641 ACGCGCCAGA CCCCCATCT ATAGGCCTAT CATTGTGCTC AACCACACA ATGAAAAAAT

FIG.11A-11

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29701 TCATAGATTG GACGGTCTCA AACCATGTTT TCTTCTTTA CAGTATGATT AAATGAGACA  
 29761 TGATTCTCTG AGTCCTTATA TTATTGACCC TTGTTGCGCT TTTCTGTGCG TGCTCTACAT  
 29821 TGCGTCGGGT CGCTCACATC GAAGTAGATT GCATCCACCC TTTCACAGTT TACCTGCTTT  
 29881 ACGGATTTGT CACCCTTATC CTCATCTGCA GCCTCGTCAC TGTAGTCATC GCCTTCATTG  
 29941 AGTTGACATTG ATCGGATTTGT GTGCGCATTT CGTACCTTAG GCACCATCCG CAATACAGAG  
 30001 ACAGGACTAT AGCTGATCTT CTCAGAATTC TTTAATTATG AAACGGATTG TCACTTTTGT  
 30061 TTTGCTGATT TTCTGCGCCC TACCTGTGCT TTGCTCCCAA ACCTCAGCGC CTCCCAAAAG  
 30121 ACATATTTCC TGCAGATTCA CTCAAATATG GAACATTCCT AGCTGCTACA ACAAACAGAG  
 30181 CGATTTGTCA GAAGCCTGGT TATACGCCAT CATCTCTGTC ATGGTTTITTT GCAGTACCAT  
 30241 TTTTGGCCTA GCCATATACC CATACCTTGA CATTGGTTGG AATGCCATAG ATGCCATGAA  
 30301 CCACCTTACT TTCCAGCGC CCAATGTCA ACCACTGCAA CAGSTTATTG CCCCAATCAA  
 30361 TCAGCCTCGC CCCCCTTCTC CCACCCACCC TGAGATTAGC TACTTTAATT TGACAGGTGG  
 30421 AGATGACTGA ATCTCTAGAT CTAGAATTGG ATGGAATTAA CACCGAAGAC CGCCTACTAG  
 30481 AAAGGCGCAA GCGCGCGTCC GAGCGAGAAC GCCTAAACAA AGAAGTTGAA GACATGGTTA  
 30541 ACCTGCACCA GTGTAAAGA GGTATCTTTT GTGTGGTCAA GCAGGCCAAA CTTACCTACG  
 30601 AAAAAACCA TACCGGCAAC CGCCTTAGCT ACAAGTACC CACCCAGCGC CAAAACTGG  
 30661 TGCCTATTGG GGGAGAAAAA CTTATCACCG TCACCCAGCA CTCGGCAGAA ACAGAGGCT  
 30721 GCCTGCACAT CCCCTATCAG GGTCCAGAGG ACCTCTGCAC TCTTATTAAA ACCATGTGTG  
 30781 GCATTAGAGA TCTTATTCCA TTCAACTAAC AATAAACACA CAATAAATTA CTTACTTAAA  
 30841 ATCAGTCGAC AAATCTTTGT CCAGCTTATT CAGCATCACC TCCTTTCCCT CTTCCCAACT  
 30901 CTGGTATTTT AGCAGCCTTT TAGCTGCGAA CTTTCTCAA AGTCTAAATG GGATGTCAAA  
 30961 TTTCTCATGT TCTTTGCCCT CCGCACCCAC TATCTTCATA TTGTTGAGA TGAAACGCGC  
 31021 CAGACCGTCT GAAGACACCT TCAACCTGTG GTACCCATAT GACACGGAAA CCGGCCCTCC  
 31081 AACTGTGCTT TTCTTACCC CTCCCTTTGT GTCGCCAAAT GGGTTCCAGG AAAGTCCCCC  
 31141 CGGAGTGCTT TCTTTGCGTC TTTCAGAACC TTTGGTTACC TCACACGGCA TGCTTGCGCT  
 31201 AAAAAAGGG AGCGGCCGTG CCCTGGATCA GGCAGGCAAC CTTACATCAA ATACAATCAC  
 31261 TGTTTTCTCAA CCGCTAAAAA AAACAAAGTC CAATATAACT TTGGAACAT CCGCGCCCTC  
 31321 TACAGTCAGC TCAGGCGGCC TAACCATGGC CACAACCTCG CCTTTGGTGG TCTCTGACAA  
 31381 CACTCTTACC ATGCAATCAC AAGCACCCTG AACCGTGCAA GACTCAAAAC TTAGCATTTG  
 31441 TACCAAAGAG CCACCTACAG TGTTAGATGG AAAACTGGCC CTGCAGACAT CAGCCCCCTC  
 31501 CTCTGCCACT GATAACAACG CCCTCACTAT CACTGCTCA CCTCCTCTTA CTACTGCAAA  
 31561 TGGTAGTCTG GCTGTTACCA TGGAAAAACC ACTTTACAAC AACATGSGAA AACTTGGGCT  
 31621 CAAAATTTGG GTCCTTTTGC AAGTGGCCAC CGACTCACAT GCACTAACAC TAGGTACTGG  
 31681 TCAGGGGGTT GCAGTTTATA ACAATTGTCT ACATACAAAA GTTACAGGCG CAATAGGGTT  
 31741 TGATACATCT GGCAACATGG AACTTAAAC TGGAGATGGC CTCTATGTGG ATAGCGCCCG  
 31801 TCCTAACCAA AAACACATA TTAATCTAAA TACCACAAAA GGCCTTGCTT TTGACAACAC  
 31861 CGCAATAACA ATTAACGCTG GAAAAGGGTT GGAATTTGAA ACAGACTCCT CAACCGGAAA  
 31921 TCCCTAGAAA ACAAAAATTG GATCAGGCAT ACAATATAAT ACCAATGGAG CTATGGTTGC  
 31981 AAAACTTGA AGACGGCTCA GTTTTGACAG CTCGCGAGCC ATACAAATGG GCAGCATAAA  
 32041 CAATGACAGA CTTACTTCTT GGACAACACC AGACCATCC CAAATTTGCA GAATTTGCTC  
 32101 AGATAAAGAC TGCAAGCTAA CTCTGGCGCT AACAAAAATG GGCAGTCAAA TTTTGGGCAC  
 32161 TGTTCAGCT TTGGCAGTAT CAGGTAAATG AGGCTCCATC AATGGAACCT TAAGCAGTGT  
 32221 AAACCTGGTT CTTAGATTGG ATGACAACGG ABGTCTTATG TCAAAATCT CACTGGACAA  
 32281 ACAGTATTGG AACCTTAGAA ACGGGGACTC CACTAACCGT CAACCATACA CTTATGCTGT  
 32341 TGGGTTTATG CCAAACTTAA AAGCTTACCC AAAAAGCTCA AGTAAAACTG CAAAAAGTAA

FIG.11A-12

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32401 TATTGTTAGC CAGGTGTATC TTAATGGTGA CAAGTCTAAA CCATTGCATT TTACTATTAC
32461 GCTAATGGA ACAGATGAAA CCAACCAAGT AAGCAAAATC TCAATATCAT TCAGTTGGTC
32521 CTGGAACAGT GGACAATACA CTAATGACAA ATTTGCCACC AATTCTCTATA CCTTCTCCTA
32581 CATTGCCAGG GAATAAAGAA TCGTGAACCT GTTGCGATGT ATGTTTCAAC GTGTTTATTT
32641 TTCAATTGCA GAAATTTTCA AGTCATTTTT CATTCAGTAG TATAGGCCCA CCACCACATA
32701 GCTTATACTA ATCACCCTAC CTTAATCAAA CTCACAGAAG CCTAGTATTC AACCTGCCAC
32761 CTCCCTCCCA ACACACAGAG TACACAGTCC TTCTCCCGG GCTGGCCTTA AACAGCATCA
32821 TATCATGGGT AACAGACATA TTCTTAGGTG TTATATTCCA CACGGTCTCC TGTCGAGCCA
32881 AACGCTCATC AGTGATGTTA ATAAACTCCC CGGGCAGCTC GCTTAAAGTC ATGTGCGTGT
32941 CCAGCTGCTG AGCCACAGGC TGCTGTCCAA CTTGCGGTGG CTCACGGGGG GGCGAAGGAG
33001 AAGTCCACGC CTACATGGGG GTAGAGTCAT AATCGTGCAT CAGGATAGGG CGGTGGTGCT
33061 GCAGCAGCGC GCGAATAAAC TGCTGCGCGC GCCGCTCCGT CCTGCAGGAA TACAACATGG
33121 CAGTGGTCTC CTCAGCGATG ATTCGACCGC CCGCGACGAT AAGGCGCCTT GTCCTCCGGG
33181 CACAGCAGCG CACCCTGATC TCACCTTAAGT CAGCACAGTA ACTGCAGCAC AGTACCACAA
33241 TATTGTTTAA AATCCCACAG TGCAGGCGCG TGATATCCAA GCTCATGGCG GGGACACAG
33301 AACCCACGTG GCCATCATAC CACAAGCGCA GTGATATTAA GTGGGACGCC CTTAAGTTC
33361 CGCTGGACAT AAACATTACC TCTTTTGGCA TGTGTAAAT CACCACCTCC CGGTACCATA
33421 TAAACCTCTG ATTAACATG CGCGCATCCA CACCACCTCT AAACAGCTG GCCAAACCT
33481 GCCCGCGCGG TATGCACTGC AGGGAAACCG CACTGGAACA ATGACAGTGG AGAGCCGAGG
33541 ACTCGTAACC ATGATCATC ATGCTCGTCA TGATATCAAT GTTGGCACAA CACAGGCACA
33601 CGTGCATACA CTTCCCTCAGG ATTACAAGCT CCTCCCGCGT CAGAACCATA TCCCAGGGAA
33661 CAACCCATTG CTGAATCAGC GTAAATCCCA CACTGCAGGG AAGACCTCGC ACGTAACCTA
33721 CGTTGTGCAT TGTCAAAGTG TTACATTCGG GCAGCAGCGG ATGATCCTCC AGTATGGTAG
33781 CCGGTGCTC TGCTCAAAA GGAGGTAGGC GATCCCTACT GTACGGAGTG CGCCGAGACA
33841 ACCGAGATCG TGTGGTGTG AGTGTATGC CAAATGGAAC GCCGGACGTA GTCATATTTT
33901 CTGAAGCAAA ACCAGGTGCG GCGGTGACAA ACAGATCTGC GTCTCCGGTG TCGTGGCTTA
33961 GCTCGCTCTG TGTAGTAGTT GTAGTATATC CACTCTCTCA AAGCATCCAG GCGCCCCCTG
34021 GCTTCGGGTT CTATGTAAC TCCTTCATGC GCCGCTGCCG TGATAACATC CACCACCGCA
34081 GAATAAGCCA CACCCAGCCA ACCTACACAT TCGTCTCGG AGTCACACAC GGGAGGAGCG
34141 GGAAGAGCTG GAAGAACCAT GTTTTTTTTT TTATTTCCAA AAGATTATCC AAAACCTCAA
34201 AATGAAGATC TATTAAGTGA ACGCGCTCCC CTCGGTGGG GTGGTCAAACT TACACAGCCA
34261 AAGAACAGAT AATGGCATT GTAAGATGTT GCACAAATGGC TTCCAAAAGG CAAACTGCCC
34321 TCACGTCCAA GTGGACGTAA AGGCTAAACC CTTCAGGGTG AATCTCTCT ATAAACATTC
34381 CAGCACCCTT ACCATGCCCC AAATAATTTT CATCTCGCCA CCTTATCAAT ATGTCTCTAA
34441 GCAAAATCCG AATATTAAGT CGCGCAATTG TAAAAATCTG TCCAGAGGCG CCTCCACCT
34501 TCAGCCTCAA GCAGCGAATC ATGATTGCAA AAATTCAGGT TCCTCAGACA CCTGTATAAG
34561 ATTCAAAAGC GGAACATTAA CAAAATACC GCGATCCGCT AGGTCCCTTC GCAGGGCCAG
34621 CTGAACATAA TCGTGCAGGT CTGCACGGAC CAGCGCGGCC ACTTCCCGCG CAGGAACCAT
34681 GACAAAAGAA CCCACACTGA TTATGACAGC CATACTCGGA GCTATGCTAA CCAGCGTAGC
34741 CCGGATGTAA GCTTGTGCA TGGCGGCGGA TATAAATGC AAGGACTCGB CCAAAAATCT
34801 AGGCAAGGCC TCGCGCAAAA AGCAAGCAC ATCGTAGTCA TGCTCATGCA GATAAAGGCA
34861 GGTAAAGTTCC GGAACCAACA CAGAAAAAGA CACCATTTTT CTCTCAAAAC TGCTTCCGGG
34921 TTCTTGATCA AACCAAAAAT AAAATAACAA ACATTTAAAC ATTTAGAAGC
34981 TGNTTTACAA CAGGAAAAAC AACCTTATA AGCATAAGAC GGACTACGGC CATTCGGCGG
35041 TGACCGTAAA AAAACTGGTC ACCGTGATTA AAAAGCACCA CCGACAGTTC CTCGGTCAATG

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FIG. 11A-13

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35101 TCCGGAGTCA TAATGTAAGA CTCGGTAAAC ACATCAGGTT GGTAAACATC GGTCAGTGCT
35161 AAAAAGCGAC CGAAATAGCC CGGGGGAATA CATACCCGCA GGCCTAGAGA CAACATTACA
35221 GCCCCCATAG GAGGTATAAC AAAATTAATA GGAGAGAAAA ACACATAAAC ACCTGAAAAA
35281 CCTCCTGCC TAGGCAAAAT AGCACCCCTCC CGCTCCAGAA CAACATACAG CGCTTCACA
35341 GCGGCAGCCA TAACAGTCAG CCTTACCAGT AAAAAAACCT ATTAATAAAC ACCACTCGAC
35401 ACGGCACCAG CTCATCAGT CACAGTGTA AAGGGCCAA GTACAGAGCG AGTATATATA
35461 GGAATAAAAA ATGACGTAAC GGTAAAGTC CACAAAAACC ACCCAGAAAA CCGCAGCGCA
35521 ACCTACGCC AGAAACGAAA GCCAAAAAAC CCACAACCTC CTCAAATCTT CACTTCCGTT
35581 TTCACGAT ACGTCACTTC CCATTTTAAA AAAAACTAC AATTCCCAAT ACATGCAAGT
35641 TACTCCGCC TAAACCTAC GTCACCGCC CGTTCCAC GCCCCGCC ACGTCACAAA
35701 CTCCACCCC TCATTATCAT ATGGCTTCA ATCCAAAAA AGGTATATTA TTGATGATG
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FIG. 11A-14

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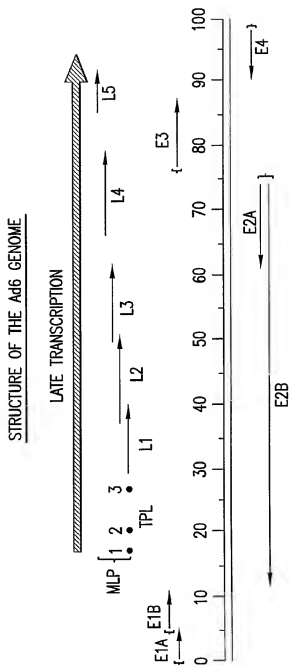


FIG.12

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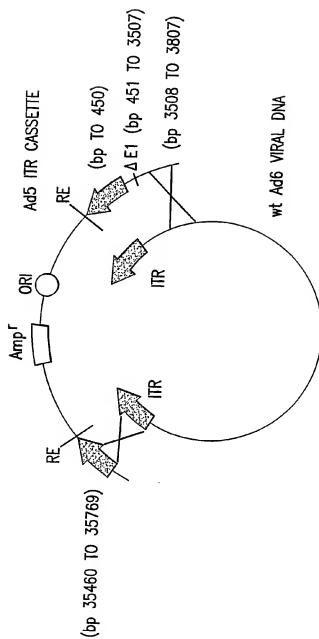


FIG.13